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ARTERIAL HYPOTENSION *

JOSEPH H. BARACH, M.D.

PITTSBURGH

It is well at times to free our minds from the fixity of things as they are and try to see an object in its actual relationship to the complete scheme of things to which that object belongs. A true perspective thus gained will occasionally save us from getting too far from the main road of travel and from going astray.

Because arterial hypertension has been so widely studied, even to the point of having quite a number of books written on the subject, arterial hypotension has likewise been trotted into the medical arena, to have its action and values carefully rated.

Whatever advance has come to medicine through the study of arterial tension, this study was only made possible by the perfected sphygmomanometer. Blood pressure instruments, as well as blood pressure studies, have rendered a signal service to medicine; and we who have used them, each model in its turn, are grateful to Stanton, Nicholson, Faught and others for their efforts in simplifying and standardizing the sphygmomanometer, and making of it a practical every day instrument, and to Norris, Goodman, Gittings and others for their valuable contributions to the subject.

A noted internist examines a patient and evaluates his disease, and an average practitioner examines a similar patient and places his estimate on the case. It is easy to surmise that there will be two widely varying diagnoses as a result of different experiences and breadth of point of view. On the other hand, blood pressure estimations made by the same examiners of totally unequal medical skill will give the same result and have exactly the same scientific value.

One may therefore say that a procedure, no matter how limited its scope, which makes the effort of the most experienced, and that of the average physician of equal scientific value, is advantageous to medicine. Instruments of precision are democratizing the practice of medicine very rapidly. We need more instruments, more methods of precision, more criteria, and more standardization; but, above all, we need correct interpretation of the data furnished by these methods. Great clinical

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insight will ever remain the genius of a few. But of what good is the science of medicine if it does not reach all the sick in the time of their need?

Arterial tension of a certain height, however produced and maintained, is necessary for propulsion of the blood. Sir James Barr [1] has well said, "Without a certain diastolic pressure, man could not assume and maintain the erect posture. If you hang a rabbit by the ears, after the sympathetic nervous system has been divided in the neck, it immediately dies because all the blood gravitates into the abdomen. Only for the resistance created to the outflow, by the vasomotor nerves, man would have to go on all fours."

It is well then, since there is arterial tension, hypertension and hypotension, that we learn its full significance and what there is for us to do about it.

My discussion deals with arterial hypotension. For a more complete understanding and a broader view of the subject as a whole, I shall present for your consideration some observations on low blood pressure, both in health and disease. For the sake of uniformity with the work of others, I have adopted the level of 110 mm. of mercury or less as indicating arterial hypotension. Having agreed that 110 mm. of mercury is the high point of arterial hypotension, we may ask ourselves first of all, What is the frequency of hypotension in health? In answer to this, one should examine healthy groups to determine the incidence of this condition.

RESULTS OF EXAMINATIONS

Group 1.—In 1914, at Carnegie Institute of Technology, Pittsburgh, we made a study [2] of blood pressures in 656 students. In this series, we found twenty-three cases in which the systolic pressure was from 100 to 110 mm. of mercury, and seven in which the systolic pressure was from 90 to 100 mm. of mercury. This made a total of thirty cases of hypotension in 656 normals, which was an incidence of about 4 per cent.

Group 2.—In the summer of 1918, at Camp Sherman, out of a series of 31,596 recruits, 1,315 were referred to our cardiovascular board for special study. In this group of 1,315, there were seventy-three cases of pure arterial hypotension. This hypotension group did not include cases of any recognized cardiovascular or other organic disease. Of these seventy-three cases, we found it necessary to reject thirteen

1. Barr, James: High Arterial Pressure, Its Nature, Causes, Effects and Treatment, Am. Med. **29**:349 (June) 1923.

2. Barach, J. H., and Marks, W. L.: Blood Pressures, Their Relation to Each Other and to Physical Efficiency, Arch. Int. Med. **13**:648-655 (April) 1914.

with the diagnosis of arterial hypotension, believing that those men were incapable of performing the duties of a soldier. The incidence of hypotension for the group was about 5.5 per cent.

Group 3.—In this group of 27,224 recruits, 1,016 were examined by our board. Of these, twenty-four were rejected as in Group 2, an incidence of about 2.3 per cent.

Group 4.—In the examination of last year's freshmen at the Carnegie Institute of Technology, Dr. Wm. L. Marks and I [2] examined the records of 1,100 males. In this 1,100, we found that fifteen had a systolic pressure of 110 mm. of mercury and nine had a systolic pressure

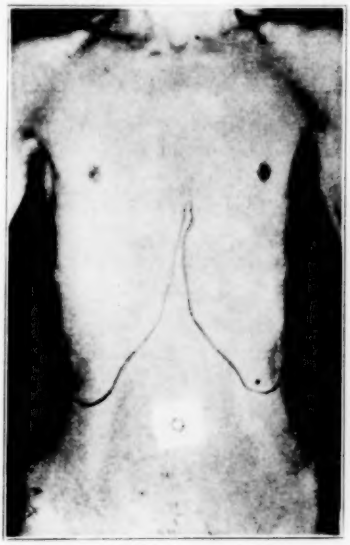

Fig. 1.—Asthenic type; hypotension, 68 per cent.

of less than 110 mm. of mercury. Again, we find an incidence of about 2.5 per cent.

The body weight of these hypotension patients was considerably less than that of the other men. Compared to standard body weight, seventeen out of the twenty-four averaged 16 pounds (7.3 kg.) under normal for their age and weight. Two were normal, and five out of the twenty-four were 5 pounds (2.3 kg.) above normal. This underweight indicates the type of individual in whom hypotension occurs.

Another characteristic of the type is found in the chest expansion, which was 2.9 inches (7.2 cm.) for the hypotension patients while it was 3.1 inches (7.8 cm.) for the normals.

Fig. 2.—Sthenic type; hypotension, 9.7 per cent.

Fig. 3.—Hypersthenic type.

Group 5.—I now present a group illustrating the physical efficiency of this type of case. In 1910, we made a study of fifty-five Marathon runners.[3] There were three cases of hypotension. While all the contestants trained for a period of months prior to the race, we found that, in the three hypotension cases, one contestant dropped out within the first few miles of the race; another ran 10 miles and quit, and the third ran 13 miles and quit, showing the physical incapacity of these hypotension subjects. Two of these three were under normal weight. The losers as well as the hypotension subjects had smaller chest capacities than the winners. In rating the physical efficiency of the fifty-five contestants, the hypotension subjects were awarded forty-third, fiftieth and fifty-first place.

Gordon, Levine and Wilmaers [4] recently reported their observations on a group of Marathon runners in Boston. In going over their figures pertaining to vital capacity, it is to be noted that with the height formula of Hewlett and Jackson as an index of vital capacity, the vital capacity of the first to finish the race was above normal. Subdivided in groups of ten, we note that the vital capacity of the first ten to finish the race was 106.7 per cent. of normal. The second ten was 106.3 per cent. of normal; the third was 104.3 per cent. of normal. While the figures are not much above normal, they do indicate the tendency.

ANALYSIS OF RESULTS

Including the five groups, we see that arterial hypotension occurred in about 3.5 per cent. of the 4,142 men of student and military age. Alvarez,[5] in a group of 6,000 men students in California of the same ages as our students, reports an incidence of 2.2 per cent. We found hypotension subjects to be considerably under normal weight. Fisk [6] of the Life Extension Institute noted underweight to be the predominant characteristic in 70 per cent. of the hypotension subjects picked out of a group of 17,000 insurance risks. Symonds,[7] reviewing a large group of 150,419 insurance risks, observed that lighter built groups have lower blood pressures than heavier ones. We found that hypotension

3. Barach, J. H.: Physiological and Pathological Effects of Severe Exertion on the Circulatory and Renal System, Arch. Int. Med. **5**:382-405 (April) 1910. Savage, W. L.; Boyce, J. W., and Barach, J. H.: Physiological and Pathological Effects of Exertion, Am. Physical and Education Rev. **15**, December, 1910; **16**, January, February, March, April, May, 1911.

4. Gordon, B.; Levine, S. A., and Wilmaeds, A.: Observations on a Group of Marathon Runners With Special Reference to the Circulation, Arch. Int. Med. **33**:425 (April 15) 1924.

5. Alvarez, W. C.; Wulzen, R., and Mahoney, L. J.: Blood Pressures, Arch. Int. Med. **32**:17 (July) 1923.

6. Fisk, E. L.: The Relationship of High Blood Pressures to Other Impairments, Am. Med. **29**:446 (June) 1923.

7. Symonds, B.: Blood Pressure in Health (Mutual Life Insurance Company, New York) Am. Med. **29**:408 (June) 1923.

patients have a smaller chest capacity. Our observations also show that hypotension patients display a marked inefficiency for arduous and sustained physical effort, and that they are distinctly of the nonathletic type. In the Boston runners referred to, the vital capacity was smaller in the third group of ten, who finished last.

At this point, I wish to call attention to the observations of Larimore [8] who made a study of a group of 417 male and female factory workers, whom he divided into four types: the sthenic, hypersthenic, hyposthenic and asthenic. Hypotension was present in 9.7 per cent. of the sthenic males, and in 68 per cent. of the asthenic males; in 18.8 per cent. of the sthenic females, and in 64.5 per cent. of the asthenic females.

We may therefore say that, among normals, hypotension occurs in lighter weight individuals of the hyposthenic and asthenic build having smaller chest capacity, and in those who are distinctly of the nonathletic type.

PHYSIOLOGIC VARIANTS PRODUCING LOWER ARTERIAL TENSION

It is well known that, on reaching high altitudes, a series of circulatory changes take place. There is adjustment and readjustment of the respiration and circulation. These changes are produced by lack of oxygen, the result of lowered partial pressure of oxygen.

Likewise, at any altitude, in a closed system, such as a breathing apparatus, or in a closed chamber, reduction of oxygen supply will bring on all the symptoms of altitude sickness: dizziness; visual disturbances; depression of the nervous system; cyanosis; weakness and exhaustion; headache; nausea; vomiting; thoracic oppression; rapid pulse; air hunger; a temporary rise and then a fall of blood pressure. These symptoms come on with varying rapidity, depending on the physical condition of the subject.

Along with these symptoms of altitude sickness, Greene and Gilbert [9] have shown by numerous electrocardiographic studies that oxygen want produces a depression of cardiac function. Rhythm production and rhythm conduction both are interfered with when the oxygen supply falls to a certain level.

A fact well known, clinically, is that the sthenic, the broad chested, the athletic type of individual adjusts himself to oxygen want quite well,

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8. Larimore, J. W.: A Study of Blood Pressure in Relation to Types of Bodily Habitus, Arch. Int. Med. **31**:567 (April) 1923.

9. Greene, C. W., and Gilbert, N. C.: Studies on the Responses of the Circulation to Low Oxygen Tension, III, Changes in the Pacemaker and in Conduction During Extreme Oxygen Want as Shown in the Human Electrocardiogram, Arch. Int. Med. **27**:517-557 (May) 1921; V, Stages in Loss of Function of the Rhythm Producing and Conducting Tissue of the Human Heart During Anoxemia, Am. J. Physiol. **56**:475 (July) 1921.

whereas the asthenic type, the hypotension type, stands it poorly. The first effect of the higher altitude on blood pressure is an increase. When readjustment has occurred, a sustained increase in pressure is never seen. When the observations have been satisfactorily made, there is either a distinct fall or a readjustment toward the normal.

The animal organism accommodates itself remarkably well to diminished oxygen. Lovenhart [10] pointed out that if the atmospheric oxygen were reduced by half, animal life would not be interfered with noticeably, but that locomotives could not run, illuminating gas would not burn and many highly inflammable substances would be as inert as water.

HYPOTENSION IN DISEASES

Let us now turn to some observations on the occurrence of arterial hypotension in disease. Of these we will first consider our findings in the acute infectious diseases.

Typhoid Fever.—In 1905, I made a series of observations on eighty-one cases of typhoid fever.[11] The readings were made four times daily throughout the course of the disease. Hypotension was found present from beginning to end, reaching its lowest level in the fourth week of the disease. The average systolic pressure for the entire group of eighty-one cases was 93 mm. of mercury in the first week; 92 mm. in the second week; 83 mm. in the third week; 83 mm. in the fourth week; 85 mm. in the fifth week, and 90 mm. in the sixth week of the disease. As convalescence progressed, pressure returned to normal.

Influenza.—Influenza is the acute infectious disease of the northern temperate zone, in which the blood pressure seems to reach its lowest level. In September, 1918, I studied the blood pressure in a series of fifty cases of influenza at the Base Hospital, Mineola, L. I. For the entire group, the average systolic pressure was 89 mm., and the diastolic

Typical Blood Pressure Curve in Influenza

First Day	Second Day	Third Day	Fourth Day
115	92	85	112
70	60	60	70
72	60	72	72

pressure 53 mm. of mercury. The lowest systolic pressure was 72 mm., and the diastolic pressure 48 mm. of mercury. In uncomplicated cases, the pressure continued falling during the first, second and third day of the disease, and began rising on the fourth day. A typical curve is shown in the accompanying table.

10. Lovenhart, A. S.: Certain Aspects of Biological Oxidation, Arch. Int. Med. **15**:1059 (June) 1915.

11. Barach, J. H.: Blood Pressure Studies in Typhoid Fever, Penn. M. J., March 19, 1907.

The slow pulse accompanying hypotension in influenza is noteworthy. Hypotension occurs in about 3.5 per cent. of normal soldiers, but it occurs in 100 per cent. of soldiers with influenza.

Acute "Colds."—In acute infections of the upper respiratory tract, such as rhinitis and bronchitis, when the patient complains of muscle pains, chilliness, cold hands, cold feet and shivering, with a normal or subnormal temperature, if such a patient's blood pressure is taken, one will find a temporary hypotension.

Pneumonia.—In pneumonia, there is practically always a marked fall in the blood pressure; so much so that a well known rule has been formulated by Gibson to the effect that a bad prognosis is indicated if the pulse rate is higher than the figures for systolic pressure. Experience has shown that this rule is not a reliable guide; it has, nevertheless, called attention to an important phase of the disease.

It is interesting to note that in acute infectious diseases involving the respiratory tract, arterial hypotension is most marked. Even in typhoid fever, the respiratory tract is not a negligible factor. In 500 cases of typhoid fever,[12] I found symptoms and physical signs of bronchitis in 20 per cent. and pneumonia in 5 per cent. Those of us who have treated many typhoid patients have known the frequency of hypostatic congestion of the lungs.

In these acute infectious diseases there is a tendency to cyanosis: most marked in influenza, constant in pneumonia and present also in typhoid fever. In typhoid fever, it is noticeable in the dusky, fevered face, and in the bluish color under the nails. In these diseases, cyanosis and increased respiratory rate indicate the degree of respiratory deficit.

There are other acute infections, among them erysipelas and diphtheria, in which hypotension occurs and in which the mechanism is probably the same. Oxygen requirement is high in all fevers, irrespective of the type. We should keep in mind that oxygen want may be produced by a high rate of expenditure, a lower than normal oxygen intake, or both, and that oxygen deficit is the result of diminished vital capacity, a diminution of the respiratory surface, and impermeability of a diseased respiratory mucous membrane. One thing stands out clearly, and that is, that in acute infections in which hypotension occurs, we find evidences of a respiratory deficit and, therefore, of oxygen want.

HYPOTENSION IN CHRONIC DISEASES

Pulmonary tuberculosis is accompanied by a very marked degree of arterial hypotension. All observers are agreed that hypotension is

12. Barach, J. H.: Clinical Observation in Five Hundred Cases of Typhoid Fever, International Clinics **11**, Series 19, 1909.

a characteristic of the disease. The degree of hypotension is proportionate to the extent and severity of the disease. In this disease, respiratory deficit and arterial hypotension go hand in hand.

That anemias are accompanied by hypotension is well known. In Addison's disease, hypotension is said to be most marked. After cardiac decompensation has begun, blood pressure falls.

Diabetes is a disease in which we find both hypotension and hypertension. Hypertension in the type associated with sclerotic vessels and nephritis; hypotension occurs in those cases in which there has been great loss of flesh and strength, and in which there is an accompanying weakness. My records in the last eighteen months show that, in 118 cases of diabetes, forty-four had a systolic pressure of 110 mm. of mercury, forty-six had a systolic pressure of from 110 to 150 mm., and twenty-eight had a pressure higher than 150.

Hypothyroidism and those inseparable endocrine disturbances corresponding closely to the clinical picture of hypothyroidism constitute a group in this series. All patients in this group had a minus basal metabolism and showed a great tendency to hypotension, irrespective of their obesity. These patients suffer decreased oxidation, which, of course, is different from oxygen want, although the effect on arterial tension may be the same.

Of twenty-three such patients, twenty had marked hypotension. Their average basal metabolic rate was minus 10 per cent., but two thirds of them had a basal metabolism of minus 15 per cent. or more. For the series, the average systolic pressure was 99 mm. of mercury, and the diastolic was 66. The average weight for the group was 35 pounds (15.9 kg.) above normal standard.

In chronic respiratory diseases, such as tuberculosis, the patient's respiratory deficit comes from the consolidated lung and muscular weakness, both reducing pulmonary ventilation. In anemia, the oxygen carrying power of the blood is deficient. In hypothyroidism, the oxygen consumption is diminished.

ESSENTIAL VASCULAR HYPOTENSION

Let us now consider a group of 100 cases in which arterial hypotension constitutes the most marked abnormality in the individual. This type has been called essential hypotension. (The group does not include recognizable cases of severe anemia, cachexia, pulmonary tuberculosis, Addison's disease, hypothyroidism or any recognized cardiovascular diseases.)

There were, in the entire group, forty males and sixty females. Without going into a detailed analysis of symptoms, which would be endless and without profit, and without classifying the various diag-

noses that were made in these patients, and which, if proved, would probably be wrong in about one-half the cases, I am going to offer my general impression of their most marked characteristic.

Taken as a group, the subjects are distinctly undersized. They are nonathletic. They have narrow nostrils and, frequently, nasal obstructions; they have narrow chests and slender bodies. They distinctly belong to the hyposthenic and asthenic type. They have a smaller than normal chest capacity, and they have a marked tendency to muscular relaxation. Frequently, they have drooping shoulders, and they are shallow breathers. At times, we note irregular breathing. This irregular breathing is similar to the periodic type of breathing seen in newcomers to a high altitude, which is plainly due to oxygen want and is promptly relieved by oxygen inhalation.

ARTERIAL HYPOTENSION AFTER MIDDLE LIFE

In a group of forty-six patients, ranging from 60 to 90 years of age, I find that there were five whose systolic blood pressure did not exceed 110 mm. of mercury. I know that some of these had arterial hypotension for many years, and I have seen the blood pressure recede from year to year, with the advancing atrophy of muscle and subcutaneous tissues. In some individuals of this type, I believe that the oxidative process, throughout their long lives, runs on an economic basis, which would, in part, account for their longevity. It is interesting to recall that Fisher of the Northwestern Mutual Life Insurance Company found that, after middle life, hypotension patients live longer than persons whose pressure does not exceed 148 mm. of mercury.

SUMMARY AND CONCLUSION

The incidence of arterial hypotension is fairly constant, and it is found in about 3.5 per cent. of persons in apparent good health. As previously pointed out by others, the individual who has hypotension is physically subnormal and is of the hyposthenic or asthenic type. My strong impression is that he has been endowed with a poor respiratory apparatus.

A normal person subjected to a diminished oxygen supply, such as occurs at high altitudes, will have a lowering of blood pressure. If he is of the sthenic type, he adjusts himself well; if he has a poor respiratory apparatus, he is sure to experience a more or less severe attack of mountain sickness. All this can be produced artificially, in a closed chamber, by reducing the oxygen supply.

In the acute infectious diseases, especially those involving the respiratory tract, in which a respiratory deficit occurs, hypotension is found. In chronic pulmonary diseases and in certain metabolic disturbances in

which there is a subnormal oxidation, and in other diseases in which there is an insufficient volume of blood to carry oxygen, as in hemorrhage or pernicious anemia, or in which the blood is a poor oxygen carrier, we again find arterial hypotension. All the evidence, when correlated, seems to point significantly to the deduction that when there is a respiratory deficit and decreased oxidation, then we find arterial hypotension. It is an easy step forward, if one is willing to take that step, to assume that we are here dealing with a cause and its effect. If this holds good in the light of further experience and observations, then, in stating the causative factors of arterial pressure, we will write that arterial pressure is dependent on energy of the heart, the resistance in the arteries, and the quantity and character of the blood. But we will place before these and as the first factor "respiratory effort and oxygenation."

A QUANTITATIVE TEST OF DIGESTIVE PANCREATIC ACTIVITY, EASILY APPLIED CLINICALLY

TESTS FOR VOLUME OF PANCREATIC JUICE AND BILE SECRETIONS *

ANTHONY BASSLER, M.D.

NEW YORK

The value of some clinical method of estimating the digestive activity of pancreatic juice is apparent. Extraction of small portions of the duodenal contents and the testing of the return to note the presence of enzymes have been devised, but all of the methods are only qualitative, and the admixture action of the enzymes takes place outside the body instead of in vivo. For these reasons, they have not been popular. A method that called for the use of tubes filled with various substances had been suggested,[1] in which the element of error is too great for clinical purposes. Another method, much more accurate but quite impossible as a routine clinical procedure, has been devised [2] in which the three enzymes are estimated. The oil regurgitation method of Boldyreff and Volhard is not practical. The best work thus far reported has been done by Crohn,[3] and acknowledgment is made of its assistance. A method of examination is herewith described in which the secretion and admixture of pancreatic juice takes place normally and within the body, which is sufficiently accurate for clinical application, is easily and quickly carried out, and does not require much special apparatus, solutions or technical knowledge for its performance. In its application, thus far, it answers far better in noting deficient pancreatic function than the examination of feces, because shades of difference in activity are not possible of being deducted from stool examinations. In these, when the examination shows many and striated muscle fibers, steatorrhea and fatty acid crystals, the pancreas is generally markedly advanced in dysfunction. Other conditions than pancreatic disease may give positive findings, and often, in distinct pancreatic involvement, the feces tests are normal owing to enzyme activity of intestinal bacteria supplanting deficient pancreatic secretion.

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*Read before the Section on Gastro-Enterology and Proctology at the Seventy-Fifth Annual Session of the American Medical Association, Chicago, June, 1924.

1. Einhorn, Max: Agar Tubes for the Estimation of Pancreatic Ferments, M. Rec., Oct. 12, 1912.

2. McClure, C. W.; Wetmore, A. S., and Reynolds, Lawrence: New Methods for Estimating Enzymatic Activities of Duodenal Contents of Normal Man, Arch. Int. Med. **27**:706 (June) 1921.

3. Crohn, B. B.: Am. J. M. Sc. **114**:393 (March) 1913; Arch. Int. Med. **15**:581 (April) 1915.

In the development of the method suggested, much work has been done against the many difficulties that are encountered in digestion in the duodenum and laboratory procedures. There are said to be four enzymes in pancreatic juice: lipase, amylase, trypsin and rennin, the first three being important. Since rennin (the existence of which I question) is also present in the stomach (which I also question) it was not considered. The original work was done on trypsin. With pepsin in the gastric juice and the juts through the pylorus carrying this ferment and even the end products of peptones, no sharp deductions of trypsin activity could be gained, this being further confused by the unknown factor of enterokinase from the duodenal mucosa, the activator of trypsin. It was learned here, however, that in achylic stomachs, free from pepsin, that the factor of pancreatic tryptic activity was capable of converting ample amounts of native proteins for nutritive balance. Because of the occurrence of lipase solely in the pancreas, its quick ability to attack neutral fat, the steadiness with which this activity was met with, its quick secretion and in frank amounts, two years time was employed in studying and utilizing this ferment as the basis of the test. As experience multiplied, two factors persisted in bringing so much discouragement about that it was abandoned, these being the bile factor and the reversibility action of this enzyme. This left amylase, which serves as the basis of the test, and enough work has been done on it to prove it to be practical. After the thirty-second procedure of methods and tests, the following plan was found to be the most practical and is accurate within a small amount of error (not more than 5 per cent.). It may form part of a bile aspiration conducted for diagnostic or therapeutic purposes.[4]

On an empty stomach, preferably in the morning, the tip of a duodenal tube is passed into the duodenum until, by fluoroscope, it is noted that the tip is at least 10 cm., or 4 inches, beyond the pylorus, water being used to assist in accomplishing this. For this, to meet the variations in all individuals, a longer tube length than that of most duodenal tubes

4. As the peptone solution is ordinarily made, it contains an amorphous débris, and this would be confusion in an *A* or *B* fraction examined for diagnostic purposes, as Lyon suggests to be done with magnesium sulphate solution. In such an instance, I advise that the peptone solution be used instead of the magnesium sulphate, but that the peptone solution be filtered through absorbent cotton. Lots of 100 c.c. each can easily be made up, and, if sterilized, will keep well until used. The magnesium sulphate solution will give pancreatic results, but it is too variable to depend on, the food shock of peptone being a far better pancreatic stimulant. If a peptone solution is used first and, for any reason, later followed by a solution of magnesium sulphate, nausea is very liable to follow. Therefore, when starting with the peptone solution, one or several doses answer satisfactorily for the accomplishment of a complete "medical gallbladder aspiration" without using magnesium sulphate at all. Usually only one dose is sufficient for a full functional return.

is essential (tube length 1.25 meters, or 49 inches). The patient is then given an injection, through the tube, of 100 c.c. of a 5 per cent. Witte peptone solution, and five minutes is allowed for it to pass beyond the duodenum, at which time the duodenal return is aspirated by a suction bulb through a 200 or 250 c.c. intervening bottle. In a few moments, the so-called "*A* fraction" begins to flow and aspiration is continued until about 20 c.c is collected, or until the *B* fraction starts. The *A* fraction is employed in the test because this consists mostly of pancreatic juice and only a small amount of bile admixture. The *B* fraction is from the general bile passages (not necessarily only from the gallbladder) and contains less pancreatic juice than the *A*, but more bile. The *C* fraction is from the smaller bile radicals in the liver, and contains decidedly less pancreatic juice than even the *B*. The *A* fraction represents the sudden secretion of the stored-up activity of the pancreas. The more normal the gland, the greater the storage, and vice versa. The storage factor and promptitude of flow are the two factors that the test depends on for normal readings in addition to the enzyme quality of the juice secreted. Since the enzymatic action of this early return from the duodenum may change quickly, it should be tested at once. It will be found that the *A* fraction obtained in this way is strongly acid in reaction. Amylase works well in both acid and alkaline mediums, but there is a slight difference in the rate depending on the intensities. For the purpose of standardizing the test and raising the p_H value to about 7.0, the *A* fraction (or about 15 c.c. of it) should be rendered slightly alkaline with saturated solution of sodium carbonate until it just shows faint pink on mixture with a weak phenolsulphonephthalein solution, although in routine work this is not necessary. No dilution of the duodenal return is made for the test, the return being taken just as obtained plus the few drops of alkaline solution, or without.

The method employed to test the amylase content is a modification of that advanced by Smith [5] for ptyalin, and rendered applicable to conditions met with in amylase and the admixed duodenal return. The degree of enzyme activity measured is the quantity that will just cause a disappearance of iodin color producing substance, under conditions described, in 20 mg. of corn starch (Duryea) contained in 5 c.c. solution with a stabilized hydrogen-ion concentration corresponding to p_H 6.7 or the use of plain water, which has a p_H value of 7.0 and which is normal for duodenal enzyme activity, and with electrolytes furnished by the presence of 0.05 sodium chlorid. The quantity of return from the duodenum in the *A* fraction that produces this result is arbitrarily

5. Ferris, H. C.; Smith, E. E., and Graves, E. V.: J. Am. Dent. A., January, 1923.

regarded as containing one-fiftieth unit of amylase, the unit being the quantity of amylase that will digest 1 gm. of starch under conditions outlined.

TECHNIC OF TEST

The reagents are: 1. A standard starch p_H 6.7 sodium chlorid solution made up as follows:

To solution *a*, when cool, 50 c.c. of solution *b* (as mentioned above, plain water acts quite as well), and 25 c.c. of solution *c* and distilled water should be added to bring the volume of the mixture to exactly 400 c.c. This should be freshly prepared.

Solution *a* is corn starch solution. In a beaker, 2 gm. of the starch to 100 c.c. of cold distilled water should be mixed thoroughly and then heated. Under constant stirring, this should be brought to boiling and then cooled.

Solution *b* is a standard buffer solution p_H 6.7 prepared as described by Clarke;[6] 50 c.c. fifth molar acid potassium phosphate and 21 c.c. fifth molar sodium hydroxid solution are accurately delivered in a 200 c.c. volumetric flask, and the contents brought to the exact volume with distilled water.[7]

Solution *c* is a 1 per cent. sodium chlorid solution.

2. A twenty-fifth normal iodin solution, with a dropper cork in the bottle.

The reagent solution should be ready so that no time is lost in carrying out the test, because pancreatic solution is stated to lose its diastatic efficiency at room temperature at the rate of about 25 per cent. in the first twenty minutes after extraction, and 70 per cent. in three hours.[8]

The procedure is as follows:

In each of ten tubes (6 by 0.5 inches [15.2 by 1.2 cm.]) in a rack and numbered from 10 to 1, one should accurately pipet with a 1 c.c. pipet marked in hundredths, fraction *A* of the duodenal return, water and reagent as shown in the accompanying table.

6. Clark, W. M.: Determination of Hydrogen Ions, Baltimore, Williams & Wilkins Company, 1920, p. 70.

7. The p_H of the most active pancreatic digestion is about 7.0, the p_H value of water. Thus, in the absence of the buffer solution, plain water may be employed, the result being practically the same.

8. This rapid rate of loss of activity has not been confirmed in my observations, at least not with the returns from the duodenum. In many observations, the loss up to as long as six hours was negligible in returns from the duodenum, whereas with alcoholic water extracts of the pancreas it is rather rapid. Therefore, the aspirated return in the test may be examined some hours afterward even though it remain cold in the interval.

Procedure of Text

Number of tube	10	9	8	7	6	5	4	3	2	1
Duodenal return, c.c.	0.1	0.11	0.125	0.14	0.17	0.20	0.25	0.33	0.5	1.0
Water, c.c.	0.9	0.89	0.875	0.86	0.83	0.80	0.75	0.67	0.5	0.0
Reagent, c.c.	4	4	4	4	4	4	4	4	4	4
Units (author's) per 100 c.c.	20	18	16	14	12	10	8	6	4	2

When set up, shaken and ready, the rack is put in an incubator at 38 C. or a water bath for thirty minutes. The rack of tubes is then taken out; the contents of each tube is shaken; a drop of the twenty-fifth normal solution of iodin is added to each tube beginning with Tube 1; twenty minutes time is allowed for the changing of colors to become settled, and the estimation of units is made according to the furthest tube to the left that is achromic. The result is then expressed in units of pancreatic enzyme efficiency. No more than the one drop of iodin solution should be added because the more the iodin, the deeper the colors, the less definite the comparison and the less accurate the test.

Ordinarily, the tubes having the largest amounts of duodenal return will be green. This shades down from Tube 1, becoming lighter and fainter to one having a colorless content. The achromic tube represents the amount of return from the duodenum that contains one-fiftieth unit of amylase. Generally the tube to the left of this tube shows a light pink or gray and those more toward Tube 10 shade deeper into reddish purple. At the achromic zone, should the right tube be a sage green and the one to the left of it a very light pink, the achromic point would be between these two tubes. For instance, if Tube 5 were green and Tube 6 pink, the units per hundred cubic centimeters would be 11. The tube that contains the one-fiftieth unit is divided by 50, which gives the units per cubic centimeter. The calculation used is:

Units of amylase in 1 c.c. duodenal return = units amylase (pancreatic efficiency) per hundred cubic centimeters duodenal return.

For instance, in a test that shows achromic in the sixth tube:

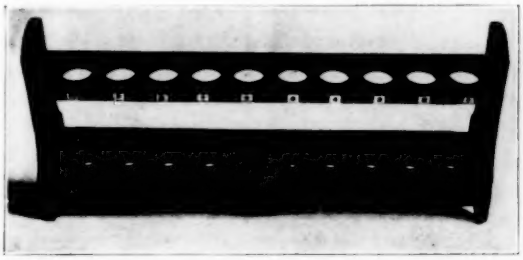
$$
\begin{array}{r|l}
 & .12 \\
\hline
50 & 6.00 \\
 & 50 \\
\hline
 & 100 \\
 & 100 \\
\hline
\end{array}
$$

$0.12 \times 100 =$ pancreatic efficiency of 12 units (author's)

It will be noted that the test is so arranged that the result in units is double the number of the tube in which the reaction occurs; thus the sixth tube equals 12 of my units.

The test, as described, takes care of most instances of low pancreatic activity, and meets clinical requirements in a routine way. Should no achromic point be present in the first tube, a greater amount of duodenal return may be used, and, according to the amount employed to arrive at the achromic point, a calculation may be made.

The test is so arranged that the extreme normal ranges occur between the fourth and the seventh tubes (from 8 to 14 units), giving sufficient tubes for errors of the gland on each side of these. The average units in normal persons are between 10 and 12, and, as experience multiplies, we find 6 units is suspiciously low (slight hypopancreorrhea). Up to the present, in even late carcinoma, marked fibrosis, or acute and suppurative pancreatitis, the test, as outlined, answered for the low unit readings. In very active secretion, the dilution may be increased and calculated accordingly. The various contents should be added to the tubes, beginning with Tube 10 on the left and working to Tube 1 on the right. This rule should be carried out to the end of the test. This preserves the proper intervals of time in the various additions. Usually, not more than ten minutes are necessary to prepare the tubes in the rack, and this need not be figured off the incubator time (thirty minutes).



Wooden test tube rack with numbers of tubes, and, below, the amounts of duodenal return, reagent and water, written so they can readily be followed. The rack is the usual form found in any laboratory, and the numbers can easily be attached.

Every method to estimate the enzymatic action of the duodenal contents must combine delicacy, uniformity, proportion of enzyme activity and accuracy of estimation. Unless a method adheres to these, it is of little value clinically. Also, it must be possible of quick performance or it would not be used as a routine in examination. The method advanced is quantitatively accurate and meets every clinical requirement. No test that does not take into consideration the change in hydrogen-ion concentration incident to the action of an enzyme being met by buffer solution serves to much value (plain water controls this accurately enough). This is as important a factor as the temperature in which the enzyme works,[9] and this is one of the main reasons why former methods have been of so little value.

9. Sorenson, S. P. L.: Biochem. Ztschr. **21**:301, 1909.

There are, no doubt, chemical and physical factors of variation in different persons, and in the same person at different times, which give different results, but, in my experience, these are not much beyond the range of the normal set for the test. Up to the present, depressing emotional factors, which can so readily affect the salivary and stomach secretions, do not seem able so definitely to depress the pancreatic and hepatic secretions, although, in a few instances, this has occurred. The pancreas and biliary apparatus in the liver are more dependent on food stimulation, and it is for this reason that any test that does not combine a food stimulant is of little value in clinical work. Thus, the testing of a return from the duodenum in which a food stimulant has not been used is of little clinical value. The peptone solution is a quick and abundant stimulant of the pancreas even when brought in contact with the mucosa well on in the third part of the duodenum. By employing the food stimulant, we obtain the storage factor of the gland, and, as a pancreas is deficient in this, it is deficient in its running secretory function. The storage factor of all gland cells during rest is the best index of the organ function and of its activity during the complete range of active secretion.

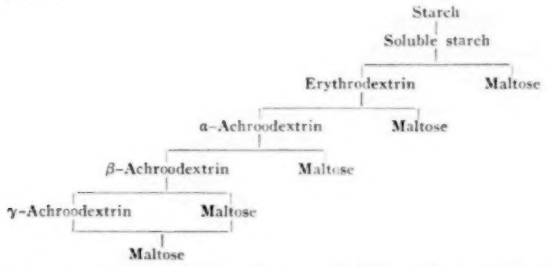
Argument may be presented that a test for amylase enzyme alone is valueless in judging the other enzymes and, in that way, the total function of the pancreas in digestive juice. Perhaps this would be true in very exceptional instances which up to the present time have not been met with in hundreds of estimations in normal and diseased pancreases. Checking the proteolytic and lipolytic activities of duodenal return against the amylolytic, with the best means on hand, shows that, within small percentages of difference, they all run together. When one is low, the other two are correspondingly diminished, and when the pancreas is functionating so that one is high, the other two also are high. This is against the assumed belief, but it is clinically true. There are two types of cells in the salivary glands and two types of cells in the gastric tubules, yet there is only one enzyme secreted by each of these organs. The pancreas, other than the spindle-shaped cells of Langerhans, which probably are concerned in internal secretion, contains only one kind of two zoned acinous cell, and it is reasonable to assume that the three enzymes or proenzymes come from this cell. It therefore follows in reason that when this cell is deficient in enzymatic power, this deficiency would be represented in all the enzymes instead of in one and not in another. Argument may be presented that an enzyme content is dependent on demands of a diet. This is true when a definite character of diet has been kept up for lengths of time, but the patients examined at the time have been on mixed meals, so this argument does not hold; and

even for people who have been on a high fat, carbohydrate or protein diet, the other enzymes than those called in demand still have been found proportional in the many tests that have been made.

Enzymes are catalyzers, that is substances capable of initiating a reaction without entering into it integrally. They are unorganized substances, usually hydrolytic in character. As a rule, they are specific. The products of the pancreatic amylase (amylopsin) on starch are the dextrins, with maltose and glucose as the end products. Because of the impossibility of preparing an enzyme and their great liability to change, their action can best be studied by in vivo methods. Each enzyme shows its greatest activity at a certain temperature, the best known having an optimal temperature between 35 and 45 C. and usually requiring a medium in reaction suitable for the enzyme. In respect to many enzymes, as with inorganic catalyzers, the intensity is almost directly proportional to the concentration of the enzyme, and the relative concentrations are directly proportional to the squares of the intensities; this is true with amylase, and has been provided for in the test. An anticatalyzer exists for amylase as for other enzymes, this being a factor in the test not possible of estimation, at this time. However, it does not seem in any way to influence the test, probably because the function of an anticatalyzer is only protective to the mucosa of the intestine from autodigestion, as the anti-enzyme (antipepsin) in the stomach protects the stomach from digesting itself, and is not active outside the body. From my studies, I believe it is possible that saliva as a digestive fluid is not absolutely essential nor a factor to consider in the test. Its action is stopped by the hydrochloric acid of the stomach, and ptyalin is not active in the duodenum. At any rate, no saliva is introduced into the duodenum, so this does not concern us in the test. The pancreatic amylase (amylopsin) is much more active than ptyalin but slower to start, is secreted in larger quantity and is active under alkaline, acid and neutral reactions. Pancreatic amylase will digest the raw starch of corn and wheat completely but potato starch only to about 80 per cent.; therefore, corn starch is used in the test. At the proper temperature and alkaline reaction conditions, marked starch conversion takes place in an hour or two. Chilling of the test tubes with ice water promptly checks amylase activity, but its activity can be restored at 40 C.; for this reason, it is often wise to chill the tubes before the twenty minutes standing.

Accompanying each dextrin, a small amount of maltose and glucose are formed, the quantity of maltose growing gradually larger as the process of transformation progresses. As each new dextrin is formed from soluble starch, a portion of maltose is formed by hydrolysis—thus,

the sugar content is difficult of estimation. Hawk graphically illustrates this as follows:



In addition to the foregoing, it is proved that with pancreatic amylase the amyloclastic tests correspond to the saccharogenic,[10] and, since they are simpler to perform and with less error in estimation of the amounts, they are to be desired in this work.

The amylase of the pancreas converts starch into dextrin more rapidly than the dextrin into maltose. Amylopsin, however, is capable of dissolving and digesting very large amounts of starch. Bile and duodenal juice do not affect the amylolytic action of pancreatic amylase, and if they do, in nonappreciable amounts. It has been reported that tests made with certain extracts of the pancreas are sometimes found which convert starch to dextrin with great speed, but which have little or no saccharifying power. For this reason, some observers seem convinced that there are at least two different enzymes in amylopsin, one an amylase which converts starch into dextrin, and one or more dextrinases which convert dextrin into maltose. It has been stated that these two enzymes are associated, but it may happen that they exist separately, or the dextrinase may be destroyed, wholly or partly, leaving the other active. As far as my observations have gone in returns from the duodenum, this is not true and need not concern us. In the test, only the first conversion of starch is estimated. With the smallest amounts of amylopsin secreted in a normal way from the pancreas, starch conversion to sugar is in steady relationship to amounts of enzyme and starch. In the enzyme digestion of the starch solution, the opalescence first disappears forming a soluble starch which gives a blue color with iodin; then erythrodextrin, which gives red with iodin; then the achroodextrins which give no color with iodin. A yellow denotes complete starch digestion in concentrated mixtures. Practically, starch contains ten chemical compounds of sugar, but, in the hydrolization, this figure does not maintain in percentages of sugar production at any

10. Sherman, H. C., and Schlesinger, M. D.: J. Am. Chem. Soc. **37**:1318 (May) 1915.

conversion period. The whole course of pancreatic starch conversion is in steady increasing percentages of sugar, glucose as well as maltose.

In the work with the various food elements and different tests, it has been proved that when the duodenum and the stomach are empty there is no secretion of pancreatic juice, or it is practically nil, and the flow of pancreatic juice keeps up only as long as food is coming through the pylorus or food is thrown into the duodenum. It is true that after a mixed meal, from two to four hours represents the maximum quantity of pancreatic juice (this being the time in which the greatest amount leaves the stomach), but the juice at this time, in a unit, is not as rich in enzyme content as the initial flow; thus, this storage factor is taken advantage of as the standard of enzyme content of the juice and gland ability, rather than the later phase of secretion.

The amylase found in the feces is no doubt derived from pancreatic juice, but whether that in the blood and in the urine also is derived from it is not positively known, although there is much reason to suppose that it is. In regard to the blood and the general body tissues, there is reason to assume that it gets into the general body from resorption into the portal blood. There is now considerable evidence to believe that this systemic content of amylase has something to do with general body nutrition, although it is impossible at present to state when subnutrition of body structure exists and the blood, stool and urine contents of amylase are low (and this also is proved in the test from the pancreas), how much is effect and how much is cause. Banting and Best have drawn attention to the importance of Langerhans' islands in the systemic combustion of sugar. There no doubt are systemic effects due to deficiency of gland function other than that produced by products of the connected islands of Langerhans. These are probably nutritional, and have been brought about by deficiency of carbohydrate conversion, resorption or hepatic cell storage ability. Apart from these are the errors of digestion due to abnormalities of function in producing clinical symptoms in the alimentary tract. Much work has still to be done, but as far as we have gone the future will warrant the use of such terms as hypopancreorrhea, hyperpancreorrhea, hypocholia and hypercholia.[11]

The theory of Solinsky, that acidity of gastric juice brought in contact with the mucous membrane of the duodenum sets up promptly a secretion of pancreatic juice, and the deduction from this that the

11. One might as well be philologically accurate when coining new terms in medicine. The new terms hypopancreorrhea and hyperpancreorrhea employed in this article are more expressive than hypopanchrea and hyperpanchrea although the latter are correct. The terms hypobilia and hyperbilia are hybrid (hyper is Greek, bilia is Latin) thus correct Greek would be expressed in the terms hypocholia and hypercholia, and these terms are recommended for use.

acidity of the gastric juice is the means that serves to inaugurate the flow from the pancreas, have not been proved in my observations in studies on lipase. This also holds good against Bayliss and Starling's belief that secretion is initiated by gastric acidity. Food substances, such as peptone and neutral oils and the starches delivered into the duodenum, do cause a prompt and vigorous pancreatic flow without acid.

The results in the test are sharp and somewhat like test meal extractions of gastric juice and more important clinically. The application of this method of examination opens up a field of interest in the most important of all digestive organs (the pancreas), which heretofore has not received much attention because of the impossibility of direct approach in examination, because proper stimulation was not employed, on account of the absence of a dependable clinical test, and because approximate in vivo methods were not employed. The test has proved that the digestive ability of the individual and the general state of nutrition largely depends on the quality of pancreatic juice or the enzyme content of the duodenum. Hypopancreorrhea is a clinical entity of no small moment. After critical analysis and considerable experience, I feel that the test deserves to become a routine of examination, and, further, that by its employment we are entering into a field of clinical development that will add distinctly to gastro-intestinal work.

ADMIXTURE FACTOR TO FOODS

It sometimes is desirable to learn what the admixture factor to foods is in the duodenum as a part of the test. A pancreatic juice may contain a greater or lesser amount of enzyme index than normal; it may be hyperfluid or diminished, and stenosis of the duct or at the ampulla may exist. In the test outlined in the above, a juice may very occasionally show a low enzyme index in a unit of return, because the return is watery compared to normal, or it may be too high because of concentration. In abnormal findings of the test described, it is well at times to find out what the admixture factor is; and, while the procedure about to be described has an element of error, it is still accurate enough for clinical purposes. For this test, when the tip of the tube is in the duodenum, the patient drinks the following mixture through a glass tube and lies on the right side. Two hundred cubic centimeters of a 5 per cent. starch solution is made up in the usual way; when cooling, 1.8 gm. of sublimed sulphur is mixed with it in a shake flask (Erlenmeyer), some large faceted beads being used to help in making the mixture uniform. This mixture will hold the sulphur in uniform suspension up to the end of the test. Having quite a flat taste, the mixture may be flavored with a few grains of saccharin and vanillin crystals.

Two Hopkins vaccine tubes are used in the test. Tube A contains part of the original starch mixture and is used as a control. Tube B contains the return from the duodenum. Each tube is filled accurately to the 5 c.c. mark and centrifugated for about two minutes at high speed. A wire with a slightly bobbed end is run down through the sulphur crystals to rearrange them, and free any bubbles or clots of starch that may have gotten in the small end. They are then centrifugated again for a minute or two, the crystals rearranged as before, and, finally, centrifugated for two minutes more. The difference between the sulphur level in the two tubes gives the admixture percentage.

Example: Tube A, 5.1 spaces; Tube B, 2.5 spaces

$$
\begin{array}{r}
\phantom{5.1\,\overline{)}}\;.49 \\
5.1\,\overline{)}\,2.500 \\
\phantom{5.1\,\overline{)}}\;204 \\
\hline
\phantom{5.1\,\overline{)}}\;460 \\
\phantom{5.1\,\overline{)}}\;459 \\
\hline
\end{array}
$$

100% — 49% = 51% admixture of duodenal contents

It must be remembered here that water and starch do not stimulate bile flow, and such flow that may be in a return is trivial. Often, when conducting this test and bile is flowing into the duodenum, as promptly as the starch solution is given by mouth, it is checked. It is better to conduct the admixture test on a subsequent day to the one for enzyme. Obviously, with an enzyme result, and a higher or lower than normal admixture result, the unit reading of enzymatic power would have to be expressed in terms of admixture, almost all of which is pancreatic juice. The range of normal for admixture is from 40 to 80 per cent., with an average normal of 58 per cent. in several hundred instances. The lengths of time for the starch to appear in the bottle is from five to fourteen minutes, with an average of six minutes, and the time for sufficient return for the tubes runs from three to twenty-five minutes, with an average of fourteen minutes. This test may be employed to diagnose stasis or obstruction in the duct of Wirsung or at the ampulla (diminished quantity of pancreatic juice with normal enzyme activity). This test is only approximately accurate.

STASIS AND OBSTRUCTION

It may be desirable at times to have some means to diagnose stasis and obstruction (partial as well as complete) in the biliary ducts. The method employed answers in this to clinical advantage. Usually this can be assumed in the ordinary medical bile aspiration when magnesium sulphate or peptone solutions are used as stimulants. A prompt bile admixture and a quick appearance of the *B* fraction denotes patent ducts. It serves the purpose at times to estimate this in a definite way, and the

method employed has been satisfactory for use. Fat is an intense stimulant to bile flow, bile being necessary for fat digestion. The patient is prepared as in the foregoing tests with the tip of the tube in the duodenum. Then about 100 c.c. of olive oil is drunk, and the patient lies on the right side. In a few minutes, a return is obtained, and 10 c.c. of this is centrifugated in a graduated centrifuge tube. The percentage of duodenal secretion in this test, almost all of which is bile, in the extreme ranges met with were 59 to 99 per cent., 84 per cent. being the average. The lower the percentage of admixture the surer we may be of the existence of stasis or obstruction in the bile passages. The bile and oil return appears from two to twenty-five minutes (average nine minutes), and a sufficient amount for the test in from seven to thirty minutes (average fourteen minutes).

The difference between the admixture result in the starch test for pancreatic juice and the oil test for bile represents bile flow, which in the normal is approximately 35 per cent. higher in the second; this 35 per cent. runs true in the low admixtures as well as in the high. Anything below 35 per cent. means either excess pancreatic secretion, too low bile secretion, or delivery (biliary stasis). This test is only approximately accurate.

METHODS OF STUDYING FAT DIGESTION

My associate, Dr. Lutz, and myself [12] have suggested methods of studying fat digestion in the human being under the microscope. If the duodenal tube is left in the duodenum some minutes longer (from ten to fifteen), the return then examined under the microscope will demonstrate these and give a fair idea of lipase activity existent in the individual, although not sufficiently accurate for clinical conclusion. One must be careful here to neutralize the return if it is acid, or the changes will not be observed.

21 West Seventy-Fourth Street.

ABSTRACT OF DISCUSSION

DR. BURRILL B. CROHN, New York: This is an era of great interest as regards functional activity and functional tests. Any addition to our knowledge on this subject, particuluarly in connection with so obscure an organ as the pancreas, is welcomed as an asset of great value. The interest in pancreatic function really goes back to the time when Dr. Einhorn first introduced the duodenal tube in this country. Previous to that event, pancreatic functional tests depended on stool examinations which were more or less inaccurate, probably more inaccurate rather than accurate. Stool examinations, as done ten years ago, were very inaccurate. It is of interest that Dr. Brown of Baltimore utilized to his own satisfaction the amylase test both in the stool

12. Bassler, A., and Lutz, J. R.: Demonstration of Human Digestion of Fat Under the Microscope, Am. J. M. Sc., December, 1924.

and in aspirated fluids from the duodenum for the purpose of studying the pancreatic ferments. In former years, it was quite common to criticize any of the pancreatic quantitative tests, on the basis that no quantitative test of pancreatic enzymes could be accurately carried out. It was pointed out that the presence of a considerable amount of saliva, gastric juice and biliary secretion so diluted the duodenal contents that no quantitative study of the pancreatic ferments would hold. In spite of the theoretical objection that the presence of four or five different fluids in the duodenum makes it difficult to get an accurate test, those who have worked on pancreatic tests through aspiraion from the duodenum have convinced themselves that this method does give valuable information. In spite of the fact that the pancreas itself furnishes a tremendous factor of safety, in spite of the fact that nine tenths of the pancreas can be destroyed without there being any physiologic evidence of pancreatic insufficiency, quantitative tests of the ferments in the duodenum are satisfactory as an index of pancreatic functional activity. I should like to endorse what the author has said about the simplicity of the methods necessary. The simpler test, such as the casein test for trypsin, the very simple Wolgemuth test of soluble starch and iodin, is very easily carried out and give accurate data. I myself found the trypsin test more accurate than the amylase test. The former I have found to be reliable and very satisfactory.

Dr. Daniel N. Silverman, New Orleans: Heretofore, the estimation of the amylase has been performed by the estimation of the end products of digestion; that is, the amount of sugar converted from the starch. But Dr. Bassler's method is an advance, in that he measures not the amount of end products, but the amount of duodenal product that is required to digest a definite quantity of mixture. This represents, as we know, only a part of the external pancreatic function as tested in various ways. I must say something in defense of the McClure method, which I have used ever since McClure advanced it, about three years ago. Dr. Denis of Tulane University of Louisiana School of Medicine and I have performed great numbers of tests on both normal and pathologic subjects. In our examination, we have followed the method of McClure in estimating three of the enzymes, and I must say that we have not been able to come to the same conclusion as that arrived at by Dr. Bassler, that the standard or the strength of the amylase will correspond to the strength of the other two enzymes, protease and lipase. Of course, the estimation of all these enzymes represents the external function of the pancreas. It has been our experience that the external function of the pancreas may be greatly inhibited and yet there be no disease whatsoever. In the severest case, it was our observation through histologic study to find that the pancreas was not involved and that the secondary disturbance was due to carcinoma of the liver and gallbladder. In accord with McClure, it is our observation that cream acts as an excellent stimulant to pancreatic secretion. We have examined fluoroscopically each and every one of our tubes in order to visualize definitely the position of the tube in the second portion of the duodenum. In the study of the duodenal contents for its pancreatic activity, the reaction of the duodenal contents has a great deal to do with the results. We find, in perfectly normal persons who are fasting, that if the duodenal contents are acid the enzymes are somewhat inhibited and sometimes absent. We have been able to check up our results of examinations through use of the duuodenal tube, by means of a fistula in man. We found that the reaction of the duodenal contents through this fistula also at times became acid.

Dr. Anthony Bassler, New York: Except to say that there is no dissociation between the enzymes, I desire to repeat that we checked up all our work with the McClure method, and the McClure method, so far as the estimation of trypsin and lipase is concerned, is valuable. I have no criticism of it, but it is as complicated and difficult to perform as a blood chemistry

examination, and that makes its use impracticable. I am now of the opinion that what we have called lipase as an enzyme, in all probability, does not exist. One can accomplish every phenomenon which I have shown you on the screen without lipase, and simply the sodium carbonate that is in the normal pancreatic secretion can produce the reduction of neutral fats. There is considerable doubt in our minds now that lipase is a ferment. In surgical work, in the study of function in connection with intestinal digestion, in metabolic or nutritional estimations, and even in diabetes, we commonly get these hypopancreatic results, and I believe that we have gone sufficiently far now with the test in cases so that we can predict a lesion in the pancreas, such as hardening of the head in chronic gallbladder disease, and up to the present we have not failed. We can say also, in many cases of cholecystitis without stone in which cholecystectomy has been done, that the symptoms in those persons are more due to hypopancreorrhea than to the gallbladder condition. Therefore, the field is a wide one, the usefulness of these findings is apparent, and again I make a plea that this test be used as a routine procedure which any one can do in forty minutes by simply following the schedule on that little rack, and I am sure that you will be as pleased as we are with the results accomplished.

BLOOD FIBRIN CHANGES IN VARIOUS DISEASES WITH SPECIAL REFERENCE TO DISEASE OF THE LIVER

JAMES S. McLESTER, M.D.
MARION T. DAVIDSON, M.D.
AND
BLANCHE FRAZIER
BIRMINGHAM, ALA.

Foster and Whipple [1] have devised a relatively simple method for the clinical estimation of fibrinogen. In their experiments on animals, these investigators have found that fibrinogen, in direct contrast to the other blood proteins, varies widely in amount, and that the production of this labile protein is stimulated in different degrees by different diseases. Whipple concludes that the liver is the chief, if not the sole, source of fibrinogen, and finds that those diseases which stimulate or depress liver function in like manner and in equal degree stimulate or depress fibrinogen production.

This suggested to us the possible clinical value of a more comprehensive knowledge of the fibrin content of the blood in disease, especially in disease of the liver, and led us to undertake a series of fibrin estimations on the blood of patients and of normal people. These first observations were reported elsewhere.[2] Our fibrin studies have been continued, and we shall here report our findings in a series of a little over 200 persons. Eighteen of these were normal controls, and thirteen had definite disease of the liver.

We have prepared a few charts designed to show the fibrin content of the blood in a number of diseases. The figures express in milligrams the amount of fibrin in 100 c.c. of plasma.

Chart 1 shows the several determinations made on normal people. It was interesting to find that the same person in health shows at all times a surprisingly constant blood fibrin. It will be noted that while these values for different individuals as shown in this chart vary somewhat, on the whole they remain, during health, within fairly narrow limits. The values for blood fibrin in health range from 250 mg. to 400 mg. per hundred cubic centimeters of plasma, with an average of about 330 mg.

From these studies, we gather the following impressions:

1. The figures for each disease with a few exceptions appear to lie fairly close together.

2. Typhoid fever and grave anemias give low values.

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1. Foster, D. P., and Whipple, G. H.: Am. J. Physiol. **58**:365 (Jan.) 1922.
2. McLester, J. S.: Diagnostic Value of Blood Fibrin Determinations with Special Reference to Disease of the Liver, J. A. M. A. **79**:17 (July 1) 1922.

3. All other diseases, no matter of what nature (except when accompanied by great liver destruction), give increased fibrin values.

4. Increased fibrin production bears no relation to the leukocyte count, for tuberculosis, chronic nephritis and myocardial disease all cause increased blood fibrin.

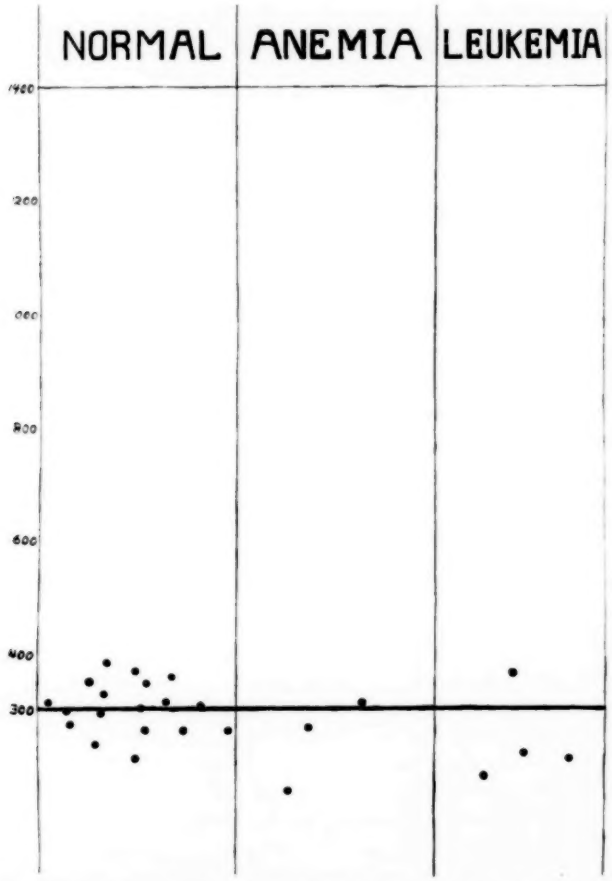

Chart 1.—Normal values uniformly adhere to the base line; anemias and leukemias show a tendency to lie below this line.

5. It is apparent that the extent and nature of the tissue injury—not an infecting organism—is the determining factor: a sterile turpentine abscess is as effective in stimulating fibrinogen production as one of septic origin.

6. The highest fibrin values are obtained in pneumonia and in septic states. Following the crisis in pneumonia or the drainage of an abscess, however, there is an immediate fall in blood fibrin.

7. Regarding the liver, one can only confirm here the observation of Whipple made on experimental animals. He found that injury or

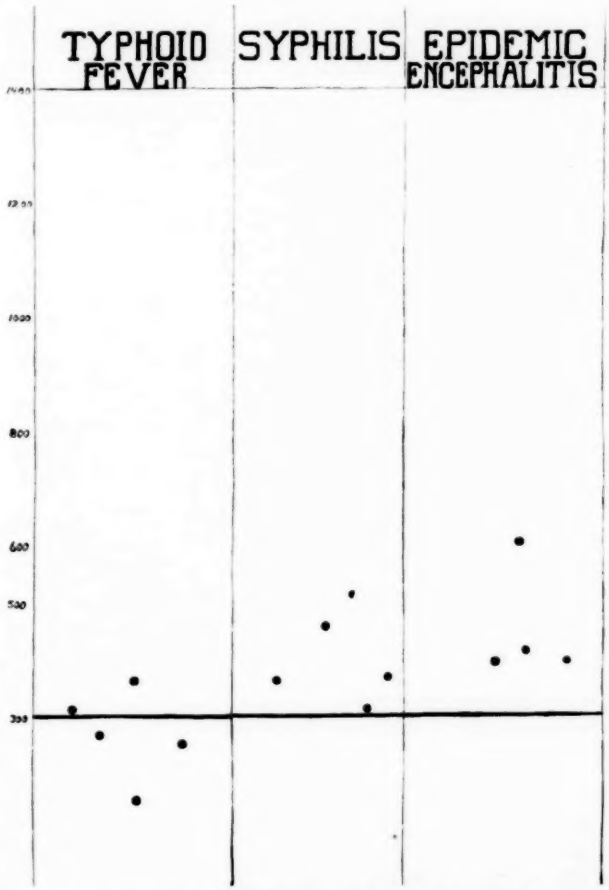

Chart 2.—The values for each disease as shown in this and the other charts lie fairly close together.

diseases which stimulate the liver are accompanied by increased blood fibrin, and that those which depress the liver or destroy a large part of its parenchyma lead to a very low blood fibrin. It would appear that the liver has a good factor of safety, and that a certain amount of its substance can be destroyed without loss of function.

The high blood fibrin seen in one instance was found in a patient who had carcinoma of the stomach with a large metastatic tumor in the liver. It is significant, however, that a preponderating amount of normal liver tissue remained. Since carcinoma in other locations stimulates fibrinogen production, and since this man retained a large amount of

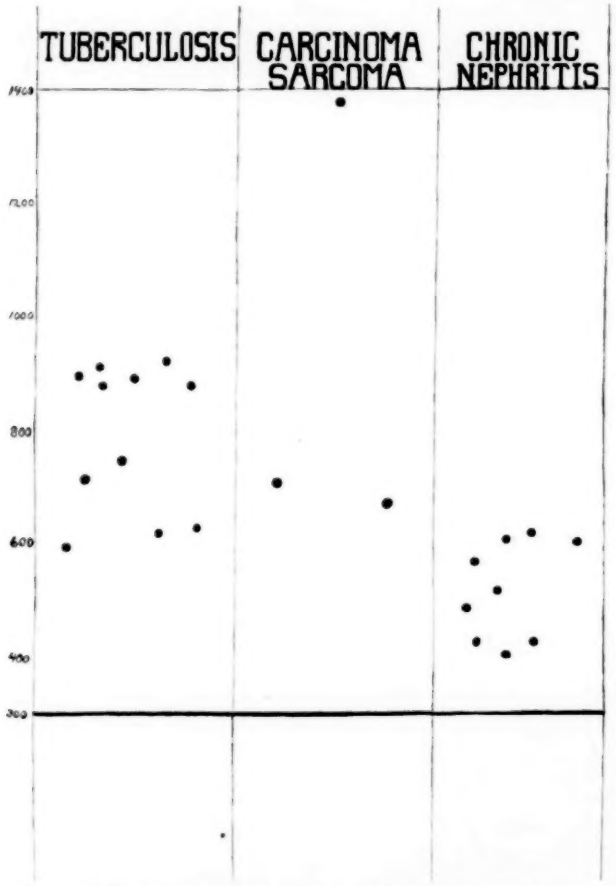

Chart 3.—Tuberculosis always shows definitely increased fibrin.

apparently normal liver parenchyma, this marked increase in blood fibrin was the logical result. On the other hand, those patients with small cirrhotic livers give correspondingly low values.

It is especially significant that the second lowest blood fibrin of the entire series was found in a patient who, at necropsy, showed extensive

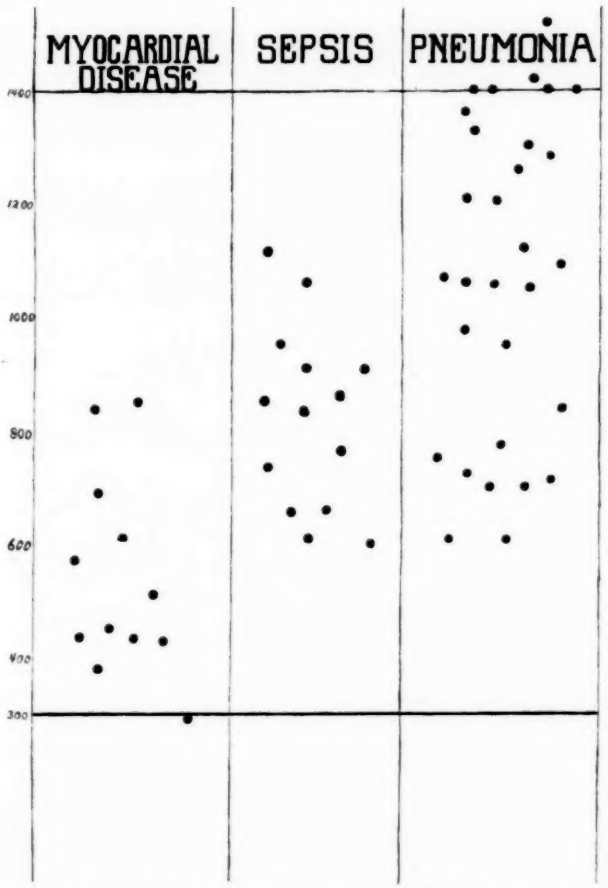

Chart 4.—High values in all septic states; especially high values in pneumonia.

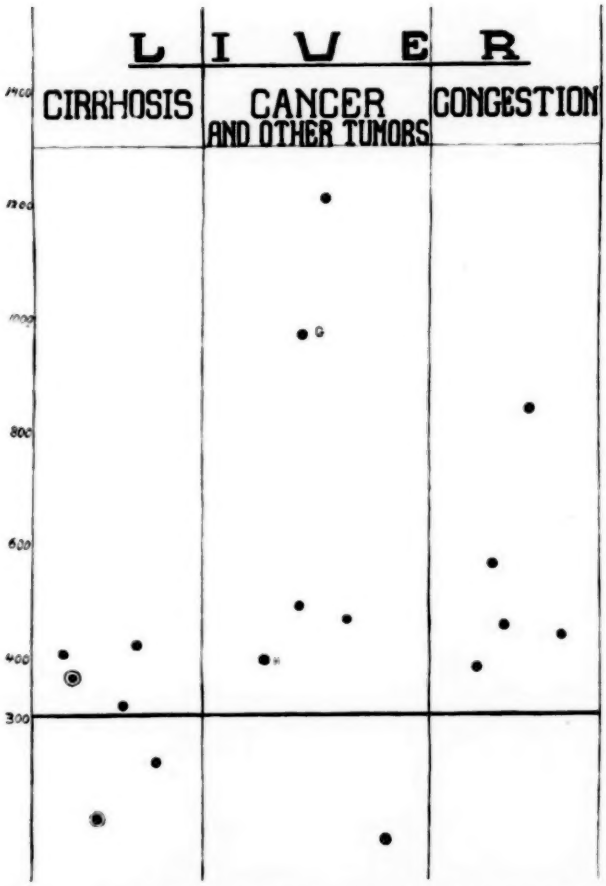

Chart 5.—Dots enclosed in a circle represent tuberculosis, one with a certain amount of cirrhosis, the other with almost complete destruction of liver substance; *G*, gastric carcinoma; *H*, Hodgkin's disease.

tuberculous destruction of the liver. Very little parenchyma remained. It is noteworthy that while tuberculosis of the peritoneum or other organs causes increased fibrin production, the reverse is true and a very low blood fibrin is found when this same process destroys a material amount of liver parenchyma. One is tempted to generalize here and to conclude, therefore, that destruction of liver parenchyma leads to impairment of the mechanism by which the body produces fibrinogen.

CONCLUSION

We realize that these studies, as they stand today, do not point to anything of immediate diagnostic value. They do show, however, certain new and interesting facts. One of these is the general fact that blood fibrin varies markedly in disease, and that the direction and extent of this deviation from the normal depends on the nature of the pathologic process. It is not unreasonable, therefore, to hope that further more intensive studies may reveal other facts of direct clinical importance.

930 South Twentieth Street.

STUDIES ON THE RESPIRATORY ORGANS IN HEALTH AND DISEASE

XIV. THE VITAL CAPACITY OF THE LUNGS OF 419 FIREMEN*

J. A. MYERS, M.D.
AND
LEROY M. A. MAEDER, M.D.
MINNEAPOLIS

The vital capacity of 419 Minneapolis firemen was secured in the present study. Of this number, 345 had been in the service of the fire department for a period of time ranging from three months to thirty-nine years and the remaining seventy-four were substitutes. The standing height was taken in every instance; the body weight was obtained in all but one man; the age in all but five; and the sitting height was secured in only 356 of the firemen. The men were all on active duty when they were measured. No sickness, either acute or chronic, was noted throughout the series.

TREATMENT OF THE DATA

Although the technical methods used in the collection of the data were accurate, the individual variability of the measurements taken was so large that the significance of the results could only be interpreted by the use of graphic and numerical analysis.

The order of procedure carried on in this study may be arranged in five groups: (1) the formation of tables showing the arithmetic averages together with the maximum and minimum values; (2) the construction of graphs showing the points of central tendency and the formation of empiric formulas by the method of weighted averages; (3) the calculation of the vital capacity and the computation of the absolute and percentage deviation of the calculated from the observed values; (4) the determination of the weighted average absolute and percentage deviants, and (5) the formation of secondary tables to show the relative increase or decrease of vital capacity.

1. *The Formation of Tables Showing the Arithmetic Averages Together with the Maximum and Minimum Values.*—Tables were made in which the vital capacity was grouped successively with the body length, stem length, body weight, age and the length of service. Field graphs

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* From the department of internal medicine and the department of preventive medicine and public health, University of Minnesota Medical School.
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were plotted, in each instance for which the vital capacity was used for the ordinate and the respective linear, temporal or ponderal determination for the abscissa. When body length or stem length were used for the abscissa, the material was divided into intervals of one-half and one-quarter inches, respectively; when age or length of service was employed, the data were arranged by yearly increments, and when body weight represented the X axis, the data were grouped into 5 pound (2.3 kg.) intervals. The weighted arithmetic average was then obtained in each group by averaging both the X and the Y values in the respective intervals. The maximum and minimum values of the vital capacity were also recorded together with the mean.

2. The Construction of Graphs Showing the Points of Central Tendency and the Formation of Empiric Formulas by the Method of Weighted Averages.—Graphs were constructed showing the general curve of the central tendency by first plotting the average vital capacities. From these averages, empiric formulas were obtained. A general inspection of the field graphs and the average points led to the assumption that an expression of the central tendency of the data could be best obtained by a straight line formula. In order to secure the best straight line formula, the method of averages was used. The general formula for a straight line is expressed by the equation: $Y = a + bX$, in which Y and X are variables and a and b are known constants. The method of averages facilitates the calculation of the constants, a and b. In order to evaluate the constants, a and b, for any given equation, the data should be divided into two equal parts, explained, in Lipka,[1] "place the sum of the residuals in each group equal to zero, i. e.,

$$\Sigma\ (r - a - bc) = 0$$

which is equal to $\Sigma\ r = na + b\Sigma c$ where n is the number of observations in the group." In calculating the equation for vital capacity against standing height, for instance, the data were divided into two groups, each containing half the total number of cases. The sum of the vital capacities (ΣY) and the sum of the body length (ΣX) were computed for each group of cases. When these equations were solved simultaneously, the values of the constants a and b were determined.

Since the numbers of cases were bunched unequally throughout this series, another step was introduced in the formation of the equations. The averages were weighted by multiplying the mean by the number of cases. In this manner, the significance of an average based on one or two cases was reduced to the same proportion as those averages calculated from many cases.

1. Lipka: Graphical and Mechanical Computation, New York, John Wiley & Sons, 1918, p. 126.

3. The Calculation of Vital Capacity and the Computation of the Absolute and the Percentage Deviations of the Calculated from the Observed Values.—After the formulas were obtained, the vital capacity

TABLE 1.—*Observed Vital Capacity of 419 Firemen Ranging in Standing Height from 63 to 78 Inches (160 to 198.1 cm.)*

Standing Height, Inches		Number of Cases	Body Weight, Pounds	Age, Years	Vital Capacity, C.c.			Length of Service, Years		Sitting Height, Inches	
Range	Mean				Maximum	Minimum	Mean	No. of Cases	Mean	No. of Cases	Mean
63.0-63.5	63.3	1	139.0	61.0	3,500	3,500	3,500	1	34.0	1	33.5
63.5-64.0	....	..	.....	....	.....	.....	.....	..	....	..	....
64.0-64.5	....	..	.....	....	.....	.....	.....	..	....	..	....
64.5-65.0	64.5	1	133.0	61.0	4,000	4,000	4,000	1	33.0	1	33.0
65.0-65.5	65.2	1	169.0	46.0	3,850	3,850	3,850	1	21.0	1	33.3
65.5-66.0	65.8	2	165.0	39.0	3,950	3,500	3,725	2	25.5	2	33.4
66.0-66.5	66.2	12	169.8	38.7	4,350	2,900	3,692	8	11.1	9	34.5
66.5-67.0	66.6	17	163.6	40.7	4,600	2,800	3,781	17	13.3	17	34.4
67.0-67.5	67.1	33	169.7	40.9	4,800	2,900	3,953	30	14.9	30	34.8
67.5-68.0	67.6	32	170.1	37.2	5,200	3,200	4,163	27	10.7	27	34.9
68.0-68.5	68.1	27	175.1	37.3	5,750	2,800	4,246	24	11.3	24	35.2
68.5-69.0	68.6	49	170.6	37.6	5,750	3,000	4,332	37	11.2	38	35.1
69.0-69.5	69.1	40	169.4	34.1	5,650	3,300	4,639	30	9.6	32	35.4
69.5-70.0	69.6	51	182.2	36.9	5,350	3,050	4,459	44	10.9	45	35.7
70.0-70.5	70.1	39	180.6	37.4	5,800	3,250	4,484	31	10.4	31	35.9
70.5-71.0	70.6	28	185.5	40.5	5,750	3,500	4,556	24	13.5	26	35.6
71.0-71.5	71.1	21	185.0	34.4	5,750	3,500	4,798	14	11.3	15	36.4
71.5-72.0	71.6	18	184.2	32.8	6,300	3,600	4,719	13	8.0	14	36.3
72.0-72.5	72.1	12	188.3	39.4	5,600	4,200	4,666	11	11.5	12	36.8
72.5-73.0	72.6	11	198.0	35.7	5,650	3,600	4,741	8	14.0	9	36.2
73.0-73.5	73.0	8	184.3	30.1	6,250	4,250	5,488	7	7.4	8	35.9
73.5-74.0	73.6	5	222.4	41.4	5,650	4,700	5,120	3	16.3	3	37.8
74.0-74.5	74.0	2	204.5	34.0	5,900	4,700	5,300	2	7.2	2	37.9
74.5-75.0	74.6	2	213.5	40.0	5,650	5,650	5,650	2	13.0	2	38.8
75.0-75.5	75.0	3	208.3	44.0	6,150	5,000	5,450	3	16.3	3	37.8
75.5-76.0	....	..	.....	....	.....	.....	.....	..	....	..	....
76.0-76.5	....	..	.....	....	.....	.....	.....	..	....	..	....
76.5-77.0	76.8	1	225.0	31.0	4,250	4,250	4,250	1	9.0	1	37.7
77.0-77.5	77.3	1	210.0	31.0	5,100	5,100	5,100	1	13.0	1	38.5
77.5-78.0	77.6	2	208.0	40.0	6,950	5,300	6,125	2	11.5	2	39.5

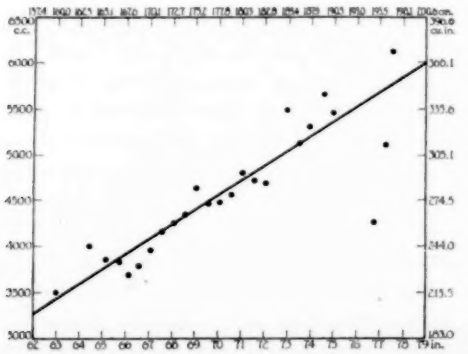

Fig. 1.—Relation between average vital capacity and standing height.

was calculated at each average point. The absolute deviation of the calculated from the observed value was then obtained and noted in tabular form. The percentage which the absolute deviant formed of the

observed value was then determined. In this way, the accuracy of the formula was estimated for each average value.

4. *The Determination of the Weighted Average Absolute and Percentage Deviants.*—The absolute and percentage deviants were weighted by multiplying them by the number of cases which they represented. These weighted deviants were then averaged by first adding them together and then dividing by the total number of cases. The average weighted deviants resulting from this procedure express the accuracy of the formula Since all formulas were obtained in a mathematical manner, the weighted average deviants are a measure of the importance of the various factors with which vital capacity is correlated.

5. *The Formation of Secondary Tables to Show the Relative Increase or Decrease of the Vital Capacity.*—The values of vital capacity were computed at regular intervals of time, length and weight. The absolute increments, the percentage increments and the percentage of the total increments for these intervals were then determined. The absolute increment represents the increase in cubic centimeters of the vital capacity for a stated unit of time, of length or of weight. A decrease of the vital capacity is a negative increment. The percentage increment is calculated by determining the precentage which the increment for any interval forms of the absolute value at the beginning of the interval. In order to determine how much of the total increase or decrease in vital capacity has occurred at any definite interval of length, weight or time, the percentage of the total increment was also calculated.

COMMENT ON RESULTS

Vital Capacity in Relation to Standing Height.—Vital capacity increases at a steady rate as the body length becomes larger (Table 1, Chart 1), and it may be expressed by the empiric formula:

$$\text{Vital capacity (cubic centimeters)} = 159.9 \text{ body length (inches)} - 6{,}655$$

The absolute vital capacity at a body length of 63 inches (160 cm.) is 3,419 c.c. This rapidly increases to 5,817 c.c. at a standing height of 78 inches (198.1 cm.), or, approximately, 160 c.c. for every inch of stature (Table 3).

As the standing height becomes greater, the body weight and the sitting height also increase in size. The age and the length of service, however, do not vary to any extent in the taller individuals.

The range of variability of the data is expressed in a rough way by the maximum and minimum values (Table 1, Chart 2). Although these quantities show a wide variation, they both increase with the

TABLE 2.—*Observed and Calculated Vital Capacity of 419 Firemen Ranging in Standing Height from 63 to 78 Inches (160 to 198.1 cm.)*

Standing Height, Inches		Observed Mean Vital Capacity	Calculated Vital Capacity	Deviation of Calculated from Observed Values	
Range	Mean	C.c.	C.c.	Cubic Centimeters	Per Cent.
63.0–63.5	63.3	3,500	3,467	— 33	— 0.94
63.5–64.0	....	.....	.....	.....	.....
64.0–64.5	....	.....	.....	.....	.....
64.5–65.0	64.5	4,000	3,659	— 341	— 8.53
65.0–65.5	65.2	3,850	3,770	— 80	— 2.08
65.5–66.0	65.8	3,725	3,866	+ 141	+ 3.79
66.0–66.5	66.2	3,692	3,930	+ 238	+ 6.45
66.5–67.0	66.6	3,781	3,994	+ 213	+ 5.63
67.0–67.5	67.1	3,953	4,074	+ 121	+ 3.06
67.5–68.0	67.6	4,163	4,154	— 9	— 0.22
68.0–68.5	68.1	4,246	4,234	— 12	— 0.28
68.5–69.0	68.6	4,332	4,314	— 18	— 0.42
69.0–69.5	69.1	4,639	4,394	— 245	— 5.28
69.5–70.0	69.6	4,479	4,474	+ 15	+ 0.34
70.0–70.5	70.1	4,484	4,554	+ 70	+ 1.56
70.5–71.0	70.6	4,556	4,634	+ 78	+ 1.71
71.0–71.5	71.1	4,798	4,714	— 84	— 1.75
71.5–72.0	71.6	4,719	4,794	+ 75	+ 1.59
72.0–72.5	72.1	4,696	4,874	+ 178	+ 3.79
72.5–73.0	72.6	4,741	4,954	+ 213	+ 4.49
73.0–73.5	73.0	5,488	5,018	— 470	— 8.56
73.5–74.0	73.6	5,120	5,114	— 6	— 0.12
74.0–74.5	74.0	5,300	5,178	— 122	— 2.30
74.5–75.0	74.6	5,650	5,274	— 376	— 6.65
75.0–75.5	75.0	5,450	5,338	— 112	— 2.06
75.5–76.0	....	.....	.....	.....	.....
76.0–76.5	....	.....	.....	.....	.....
76.5–77.0	76.8	4,250	5,625	+1,375	+32.35
77.0–77.5	77.3	5,100	5,705	+ 605	+11.86
77.5–78.0	77.6	6,125	5,753	— 372	— 6.07

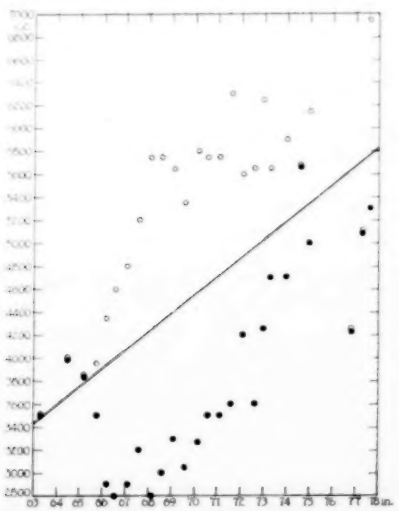

Fig. 2.—Relation between maximum and minimum vital capacity values and standing height.

growth in body length. The range of variability is approximately from one eighth to one sixth of the calculated values on each side of the curve of the central tendency.

The absolute and percentage deviants of the calculated from the observed averages (Table 2) are not unusually large except in one instance. In this case, a deviation of 30 per cent. is due to an average based on only one case.

TABLE 3.—*Changes in Calculated Vital Capacity of 419 Firemen Ranging in Standing Height from 63 to 78 Inches (160 to 198.1 cm.)*

Standing Height, Inches	Calculated Vital Capacity, C.c.	Increment		Percentage of Total Increment
		Cubic Centimeters	Percentage	
63	3,419	...	.....	.....
64	3,579	160	4.680	6.67
65	3,739	160	4.471	13.34
66	3,898	159	4.252	19.98
67	4,058	160	4.105	26.65
68	4,218	160	3.943	33.32
69	4,378	160	3.793	39.99
70	4,538	160	3.655	46.66
71	4,698	160	3,526	53.34
72	4,858	160	3.406	60.01
73	5,018	160	3.294	66.68
74	5,178	160	3.189	73.35
75	5,338	160	3.090	80.02
76	5,497	159	2.979	86.66
77	5,657	160	2.911	93.33
78	5,817	160	2.828	100.00

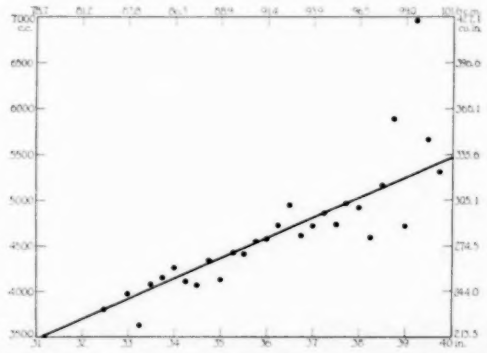

Fig. 3.—Relation between average vital capacity and sitting height.

The weighted average deviants of the vital capacity-standing height relationship are expressed in Table 16. The weighted average absolute deviant is 104.1 c.c., and the weighted average percentage deviant, 2.33 per cent. This low deviation tends to prove that a close correlation exists between vital capacity and standing height, which is more accurate than the correlation of vital capacity with any other body measurements considered in this study.

TABLE 4.—*Observed Vital Capacity of 356 Firemen Ranging in Sitting Height from 32 to 40 Inches (81.2 to 101.6 cm.)*

Mean Sitting Height, Inches	Number of Cases	Standing Height, Inches	Body Weight, Pounds	Length of Service, Years	Age, Years	Vital Capacity C.c.		
						Maximum	Minimum	Mean
32.00	1	67.5	148.0	25.0	55.0	4,475	4,475	4,475
32.25	..	.....	.....	.....	.....	.....	.....	.....
32.50	1	66.0	184.0	12.0	35.0	3,700	3,700	3,700
32.75	..	.....	.....	.....	.....	.....	.....	.....
33.00	6	67.6	144.6	13.4	36.5	4,650	3,000	3,983
33.25	2	66.4	157.0	14.0	40.5	3,850	3,200	3,525
33.50	3	67.3	144.6	21.0	50.0	4,300	3,500	4,016
33.75	11	67.9	169.0	15.1	41.1	5,500	3,500	4,136
34.00	20	68.2	159.7	13.0	39.0	5,400	2,900	4,025
34.25	17	67.6	166.6	12.8	41.2	5,150	2,900	4,100
34.50	21	68.4	171.1	14.7	40.4	5,750	3,150	4,057
34.75	18	68.5	167.8	9.8	37.0	4,950	3,200	4,319
35.00	31	68.4	168.8	11.8	39.6	5,650	3,250	4,111
35.25	22	69.1	172.7	13.7	39.6	5,350	3,150	4,405
35.50	36	69.6	179.9	12.0	36.8	6,000	2,900	4,389
35.75	29	69.0	179.0	9.7	36.8	5,750	3,200	4,546
36.00	32	69.4	179.0	9.5	33.3	5,750	2,900	4,566
36.25	25	70.1	176.0	10.7	34.4	5,500	3,700	4,712
36.50	14	70.3	188.9	9.4	33.6	6,250	3,850	4,929
36.75	14	71.0	186.9	15.8	42.4	5,600	3,500	4,586
37.00	26	71.2	203.6	12.2	36.9	5,800	3,800	4,702
37.25	4	71.6	190.8	13.9	40.7	5,800	4,150	4,838
37.50	5	71.6	194.0	13.3	39.8	5,400	4,250	4,710
37.75	2	74.7	201.5	7.0	31.5	5,650	4,250	4,950
38.00	6	71.4	199.5	7.5	35.6	5,700	3,950	4,900
38.25	2	69.9	213.5	7.7	37.0	4,750	4,400	4,575
38.50	2	76.1	196.0	10.0	40.5	5,200	5,100	5,150
38.75	2	74.5	195.5	7.7	31.5	6,150	5,900	6,025
39.00	1	73.5	280.0	9.0	29.0	4,700	4,700	4,700
39.25	1	77.8	195.0	4.5	34.0	6,950	6,950	6,950
39.50	1	74.8	216.0	9.0	30.0	5,650	5,650	5,650
39.75	1	77.5	221.0	18.5	46.0	5,300	5,300	5,300

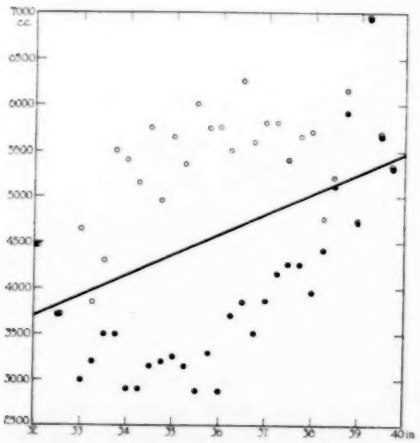

Fig. 4—Relation between maximum and minimum vital capacity values and sitting height.

Although the absolute increase in vital capacity is about 160 c.c. for each additional inch of body length (Table 3), the percentage increment or rate of increase per inch steadily falls from about 4.7 per cent. between the body lengths from 63 to 64 inches (160 to 162.5 cm.) to about 2.8 per cent. between 77 and 78 inches (195.6 to 198.1 cm.).

TABLE 5.—*Observed and Calculated Vital Capacity of 356 Firemen Ranging in Sitting Height from 32 to 40 Inches (81.2 to 101.6 cm.)*

Mean Sitting Height, Inches	Observed Mean Vital Capacity, C.c.	Calculated Vital Capacity, C.c.	Deviation of Calculated from Observed Values	
			Cubic Centimeters	Per Cent.
32.00	4,475	3,706	— 769	—17.18
32.25	.....	.....	.....	.....
32.50	3,700	3,815	+ 115	+ 3.11
32.75	.....	.....	.....	.....
33.00	3,983	3,925	— 58	— 1.46
33.25	3,525	3,979	+ 454	+12.88
33.50	4,016	4 034	+ 18	+ 0.45
33.75	4,136	4,089	— 47	— 1.14
34.00	4,025	4.144	+ 119	+ 2.96
34.25	4,100	4.198	+ 98	+ 2.39
34.50	4,057	4.253	+ 196	+ 4.83
34.75	4,319	4.308	— 11	— 0.25
35.00	4,111	4,363	+ 252	+ 6.13
35.25	4,405	4.417	+ 12	+ 0.27
35.50	4,389	4,472	+ 83	+ 1.89
35.75	4,546	4,527	— 19	— 0.42
36.00	4,566	4,581	+ 15	+ 0.33
36.25	4,712	4,636	— 76	— 1.61
36.50	4,929	4,691	— 238	— 4.83
36.75	4,596	4,746	+ 150	+ 3 26
37.00	4,702	4,800	+ 98	+ 2.08
37.25	4,838	4,855	+ 17	+ 0.35
37.50	4,710	4,910	+ 200	+ 4.25
37.75	4,950	4,964	+ 14	+ 0.28
38.00	4,900	5,019	+ 119	+ 2.43
38.25	4,575	5,074	+ 499	+10 91
38.50	5,150	5,129	— 21	— 0.41
38.75	6,025	5,183	— 832	—13.81
39.00	4,700	5,238	+ 538	+11.45
39.25	6,950	5,293	—1,657	—23.84
39.50	5,660	5,348	— 302	— 5.35
39.75	5,300	5,402	+ 102	+ 1.92

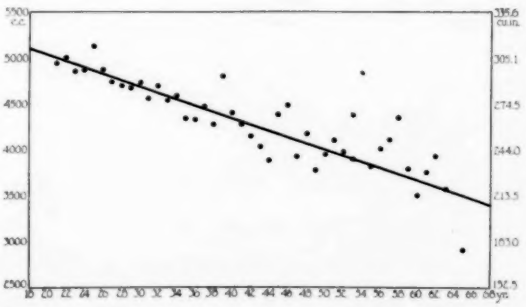

Fig. 5.—Relation between average vital capacity and age.

Twenty-five per cent. of the total increase in vital capacity between the standing heights of 63 to 78 inches (160 to 198.1 cm.) has taken place at a stature of 67 inches (170.2 cm.); 50 per cent. at a body length of 71 inches (180.3 cm.) and 75 per cent. at 74 inches (188 cm.).

Vital Capacity in Relation to Sitting Height.—Vital capacity progresses at a steady rate in unison with an increase in sitting height (Table 4, Chart 3). The growth of vital capacity in terms of stem length may be expressed by the empiric formula:

Vital capacity (cubic centimeters) = 218.9 body length (inches) — 3,299.

TABLE 6.—*Changes in Calculated Vital Capacity of 356 Firemen Ranging in Sitting Height from 32 to 40 Inches (81.2 to 101.6 cm.)*

Sitting Height, Inches	Calculated Vital Capacity, C.c.	Increment		Percentage of Total Increment
		Cubic Centimeters	Percentage	
32	3,706	...	.....	.....
33	3,925	219	5.909	12.51
34	4,144	219	5.580	25.01
35	4,363	219	5.285	37.52
36	4,581	218	4.997	49.97
37	4,800	219	4.781	62.48
38	5,019	219	4.562	74.99
39	5,238	219	4.363	87.49
40	5,457	219	4.181	100.00

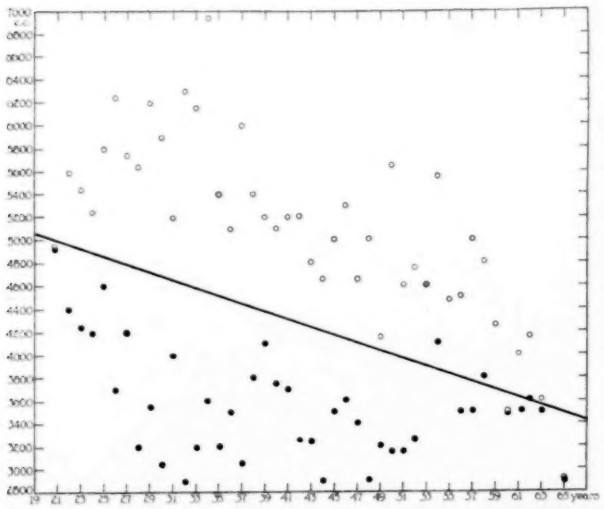

Fig. 6.—Relation between maximum and minimum vital capacity values and age.

The absolute vital capacity grows steadily larger from 3,706 c.c. at 32 inches (81.2 cm.) sitting height to 5,457 c.c. at 40 inches (101.6 cm.) — an increase of 219 c.c. per inch (Table 6).

As the stem length increases, the body weight and the standing height likewise grow larger. Age and length of service, however, are practically unchanged as the sitting height becomes longer.

TABLE 7.—*Observed Vital Capacity of 414 Firemen Ranging in Age from 21 to 65 Years*

Age, Years	Number of Cases	Body Weight, Pounds	Standing Height, Inches	Vital Capacity C.c.			Length of Service, Years		Sitting Height, Inches	
				Maximum	Minimum	Mean	No. of Cases	Mean	No. of Cases	Mean
21	1	149.0	70.3	4,950	4,950	4,950	1	1.0	1	36.7
22	2	169.0	72.0	5,600	4,400	5,000	1	0.3	2	36.1
23	2	138.0	72.0	5,450	4,250	4,850	..	.....	2	35.0
24	3	166.3	69.4	5,250	4,200	4,867	..	.....	3	35.8
25	8	158.8	69.1	5,800	4,600	5,125	5	4.5	5	36.1
26	21	173.3	69.5	6,250	3,700	4,874	18	4.6	18	35.6
27	19	178.1	69.8	5,750	4,200	4,743	16	4.9	17	35.7
28	27	171.9	69.5	5,650	3,200	4,706	21	5.1	22	35.3
29	28	178.3	69.7	6,200	3,550	4,671	24	5.4	24	36.0
30	26	178.7	69.7	5,900	3,050	4,735	21	5.7	22	35.9
31	14	182.0	70.5	5,200	4,000	4,564	14	4.9	14	35.5
32	24	183.4	69.9	6,300	2,800	4,693	14	6.5	14	35.8
33	18	172.5	68.7	6,150	3,200	4,542	15	6.2	16	35.7
34	15	173.0	69.9	6,950	3,600	4,560	14	6.3	14	35.8
35	26	172.9	68.8	5,400	3,200	4,343	21	9.0	22	35.2
36	11	176.2	69.2	5,100	3,500	4,336	10	8.0	10	35.0
37	11	178.5	69.4	6,000	3,058	4,473	7	7.5	7	35.3
38	10	186.5	69.4	5,400	3,800	4,285	9	12.1	9	35.7
39	3	171.0	72.1	5,200	4,100	4,800	2	13.5	2	37.0
40	6	178.5	69.1	5,100	3,750	4,408	6	13.5	6	36.0
41	6	204.6	68.7	5,200	3,700	4,283	6	13.3	6	35.8
42	11	179.7	69.5	5,200	3,250	4,150	10	14.1	10	35.7
43	8	158.6	68.4	4,800	3,250	4,044	7	17.0	7	35.2
44	10	183.9	68.3	4,650	2,900	3,890	9	17.8	9	35.2
45	6	206.7	69.7	5,000	3,500	4,383	4	14.8	4	36.7
46	10	215.2	69.9	5,300	3,600	4,482	8	17.9	8	35.8
47	5	188.6	69.6	4,650	3,400	3,920	5	14.7	5	35.7
48	9	180.2	69.8	5,000	2,900	4,189	8	18.8	8	35.6
49	5	176.6	68.9	4,150	3,200	3,770	2	18.8	2	34.7
50	10	195.4	69.1	5,650	3,150	3,960	9	18.9	9	35.6
51	10	183.3	69.5	4,600	3,150	4,105	9	22.3	9	35.6
52	7	172.1	68.6	4,750	3,250	3,971	7	25.6	7	34.9
53	6	171.2	69.3	4,600	2,800	3,908	5	22.4	5	35.0
54	2	219.0	71.0	5,550	4,100	4,825	2	22.0	2	36.0
55	4	178.0	68.1	4,475	2,900	3,819	3	24.0	3	33.8
56	5	171.2	69.0	4,500	3,500	4,010	5	29.2	5	35.3
57	4	187.8	70.1	5,000	3,500	4,112	4	24.5	4	35.6
58	3	167.0	69.7	4,800	3,800	4,350	2	16.4	2	35.4
59	5	185.4	69.0	4,250	2,900	3,780	5	31.6	5	35.4
60	2	167.0	69.4	3,500	3,500	3,500	2	28.5	2	36.4
61	4	164.8	66.7	4,000	3,500	3,750	3	31.7	3	34.1
62	3	184.3	69.2	4,150	3,600	3,933	3	32.3	3	35.4
63	3	195.7	70.1	3,600	3,500	3,567	3	35.0	3	34.7
64	..	.....	....	.....	.....	.....	..	....	..	....
65	1	202.0	66.0	2,900	2,900	2,900	1	24.0	1	34.3

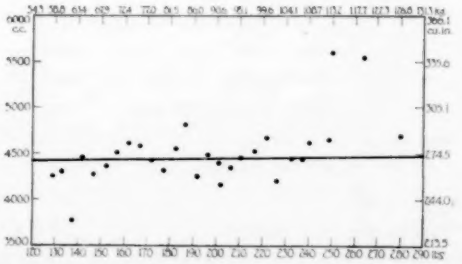

Fig. 7.—Relation between average vital capacity and body weight.

The range of variability, as shown by the maximum and the minimum values (Table 4, Chart 4), shows a wide variation. Both the maximum and minimum values increase with a growth in the stem length. The range of variability is about one eighth to one sixth of the calculated values on both sides of the central tendency curve.

The absolute and percentage deviations of the calculated from the observed averages are shown in Table 5. In the case of six average points in this table, the percentage deviations are more than 10 per cent. In all of them, however, the cases from which the averages were obtained numbered only one or two.

The weighted average deviants of the vital capacity-stem length formula are expressed in Table 16. The weighted average absolute deviant is 112.8 c.c. and the weighted average percentage deviant, 2.53 per cent.; this shows a close correlation between vital capacity and stem length. It was not possible, however, to fit the data quite so closely to the empiric formula as in the case of the body length.

The percentage increment or the rate of increase in the vital capacity grows steadily less as the stem length becomes longer (Table 6). The percentage increment is about 5.9 per cent. between a sitting height of from 32 to 33 inches (81.2 to 82.8 cm.) and falls to 4.2 per cent. between 39 and 40 inches (98.5 and 101.6 cm.).

Twenty-five per cent. of the total increase in vital capacity between the stem length from 32 to 40 inches (81.2 to 101.6 cm.) occurs at a sitting height of 34 inches (86 cm.), 50 per cent. at a height of 36 inches (91.4 cm.) and 75 per cent. at 38 inches (96.4 cm.).

Vital Capacity in Relation to Age.—Vital capacity decreases steadily as the age of an individual becomes greater (Table 7, Chart 5). It may be expressed by the empiric formula:

Vital capacity (cubic centimeters) = 5,725 — 34.46 times age (years).

The absolute vital capacity decreases steadily from 5,036 c.c. at 20 years to 3,485 c.c. at 65 years, or approximately 172 c.c. every five years (Table 9).

As the age becomes greater, the standing and the sitting heights of the individuals in this series remains about the same. Vital capacity increases very rapidly with standing height and stem length. On the other hand, it decreases with advancing age. Since the relationship between standing height or sitting height and age remains practically unchanged, at least two factors must influence the vital capacity: (1) the growth of the lungs, and (2) the loss in elasticity of the alveolar walls. The increase of vital capacity in relation to a growth in body length and stem length is undoubtedly due to an actual growth of the lung while the decline of vital capacity with age is due in all probability

TABLE 8.—*Observed and Calculated Vital Capacity of 414 Firemen Ranging in Age from 21 to 65 Years*

Mean Age, Years	Observed Mean Vital Capacity, C.c.	Calculated Vital Capacity, C.c.	Deviation of Calculated from Observed Values	
			Cubic Centimeters	Per Cent.
21	4,950	5,001.3	+ 51.3	+ 1.04
22	5,000	4,966.9	— 33.1	— 0.66
23	4,850	4,932.4	+ 82.4	+ 1.70
24	4,867	4,898.0	+ 31.0	+ 0.64
25	5,125	4,863.5	—261.5	— 5.10
26	4,874	4,829.0	— 45.0	— 0.92
27	4,743	4,794.6	+ 51.6	+ 1.09
28	4,706	4,760.1	+ 54.1	+ 1.15
29	4,671	4,725.7	+ 54.7	+ 1.17
30	4,735	4,691.2	— 43.8	— 0.93
31	4,564	4,656.7	+ 92.7	+ 2.03
32	4,693	4,622.3	— 70.7	— 1.51
33	4,542	4,587.8	+ 45.8	+ 1.01
34	4,590	4,553.4	— 36.6	— 0.80
35	4,343	4,518.9	+175.9	+ 4.05
36	4,336	4,484.4	+148.4	+ 3.42
37	4,473	4,450.0	— 23.0	— 0.51
38	4,285	4,415.5	+130.5	+ 3.05
39	4,800	4,381.1	—418.9	— 8.73
40	4,408	4,346.6	— 61.4	— 1.39
41	4,283	4,312.1	+ 29.1	+ 0.68
42	4,150	4,277.7	+127.7	+ 3.08
43	4,044	4,243.2	+199.2	+ 4.92
44	3,890	4,208.8	+318.8	+ 8.20
45	4,388	4,174.3	—208.7	— 4.76
46	4,482	4,139.8	—342.2	— 7.63
47	3,920	4,105.4	+185.4	+ 4.73
48	4,189	4,070.9	—118.1	— 2.82
49	3,770	4,036.5	+266.5	+ 7.07
50	3,950	4,002.0	+ 52.0	+ 1.32
51	4,105	3,967.5	—137.5	— 3.35
52	3,971	3,933.1	— 37.9	— 0.95
53	3,908	3,898.6	— 9.4	— 0.24
54	4,825	3,864.2	—960.8	—19.91
55	3,819	3,829.7	+ 10.7	+ 0.28
56	4,010	3,795.2	—214.8	— 5.36
57	4,112	3,760.8	—351.2	— 8.54
58	4,350	3,726.3	—623.7	—14.34
59	3,780	3,691.9	— 88.1	— 2.33
60	3,500	3,657.4	+157.4	+ 4.48
61	3,750	3,622.9	—127.1	— 3.39
62	3,933	3,588.5	—344.5	— 8.76
63	3,567	3,554.0	— 13.0	— 0.36
64	.....	3,519.6	.....	.....
65	2,900	3,485.1	+585.1	+20.18

TABLE 9.—*Changes in Calculated Vital Capacity of 414 Firemen Ranging in Age from 20 to 65 Years*

Age, Years	Calculated Vital Capacity, C.c.	Decrement		Percentage of Total Decrease
		Cubic Centimeters	Percentage	
20	5,036	.....	.....	.....
25	4,864	—172	—3.415	+ 11.09
30	4,691	—173	—3.557	+ 22.24
35	4,519	—172	—3.667	+ 33.33
40	4,347	—172	—3.806	+ 44.42
45	4,174	—173	—3.980	+ 55.58
50	4,002	—172	—4.121	+ 66.67
55	3,830	—172	—4.298	+ 77.75
60	3,657	—173	—4.517	+ 88.91
65	3,485	—172	—4.703	+100.00

to the loss of elasticity in the walls of the alveoli. With these facts in mind, it is possible to predict that the tall youth will have the greatest vital capacity while the old man who is short of stature will have the least.

When body weight is averaged by years, no definite relationship between weight and age is apparent. If, however, the length of service in the fire department is related to age, a very definite correlation is obtained, the length of service increasing strikingly with advanced age.

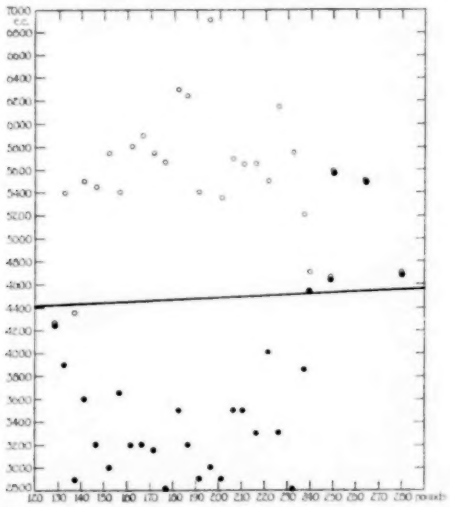

Fig. 8.—Relation between maximum and minimum capacity values and body weight.

The range of variability as shown by the maximum and minimum values (Table 7 and Chart 6) shows wide variation. This variability ranges from about two fifths to one tenth of the calculated values on both sides of the central tendency curve.

The absolute and percentage deviations of the calculated from the observed averages are listed in Table 8. In only two instances were the percentage deviants more than 10 per cent., one average representing three cases and the other two.

The weighted average deviants of the vital capacity-age formula are given in Table 16. The weighted average absolute deviant is 116.2 c.c. and the weighted average percentage deviant, 2.69 per cent. The empiric formula, therefore, is practically as accurate as it was for body length and for stem length.

The percentage increment for five year periods grows steadily greater as the age increases (Table 9). The percentage increment is about 3.4 per cent. between 20 and 25 years and becomes 4.7 per cent. between 60 and 65 years.

A third of the total decrease in vital capacity during the age intervals of 20 to 65 years occurs by 35 years and two-thirds by 50 years.

Vital Capacity in Relation to Body Weight.—Vital capacity is practically unaffected by an increase of body weight (Table 10 and Chart 7). There is a very slight rise in vital capacity with increasing weight, although the increase is so small that it falls within the margin of error. The vital capacity-body weight relationship can be expressed by the formula:

Vital capacity (cubic centimeters) $= 0.46$ times body weight (pounds) $+ 4{,}350$.

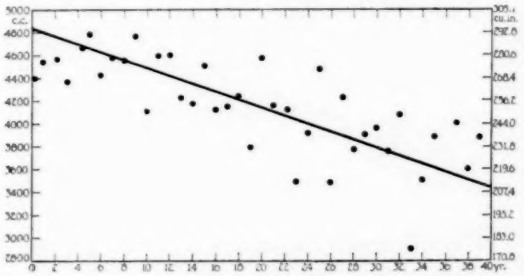

Fig. 9.—Relation between average vital capacity decrease and length of service in the fire department.

The absolute vital capacity increases steadily but very slightly from 4,405 c.c. at 120 pounds (54.4 kg.) of body weight to 4,479 c.c. at 280 pounds (127 kg.) — a total increase of 74 c.c. and an absolute increase of only 4.6 c.c. for every 10 pounds (4.5 kg.) of body weight.

As the body weight becomes heavier, the standing and sitting height becomes longer. The vital capacity, however, does not follow the advance in weight even though it is accompanied by an increase in the standing and sitting height. This is probably due to the fact that lung growth accompanies the growth of the body in length. Increase in body weight, however, above the age of 21, is brought about to a large degree by subcutaneous and visceral fat deposits. The lung receives none of this additional weight, and, consequently, the vital capacity remains practically the same even when the body weight increases.

There is no constant relationship between body weight and age in this small series of cases.

TABLE 10.—*Observed Vital Capacity of 418 Firemen Ranging in Body Weight from 125 to 285 Pounds (56.7 to 129.3 kg.)*

Body Weight, Pounds		Number of Cases	Standing Height, Inches	Age, Years	Vital Capacity, C.c.			Length of Service, Years		Sitting Height, Inches	
					Maximum	Minimum	Mean	No. of Cases	Mean	No. of Cases	Mean
Range	Mean										
125-130	129.0	1	67.0	35.0	4,250	4,250	4,250	1	12.0	1	33.8
130-135	132.7	6	67.6	38.2	5,400	3,900	4,258	6	16.0	6	33.8
135-140	137.3	9	67.5	42.7	4,350	2,900	3,767	8	16.4	8	34.3
140-145	141.6	10	67.9	35.9	5,500	3,600	4,450	8	11.1	9	34.8
145-150	146.6	21	68.3	36.1	5,450	3,200	4,268	19	10.5	19	34.7
150-155	152.1	32	68.8	34.7	5,750	3,000	4,365	23	10.8	23	35.1
155-160	156.5	28	68.9	34.4	5,400	3,650	4,504	22	8.9	25	35.2
160-165	161.8	31	69.1	34.1	5,800	3,200	4,603	29	8.7	29	35.4
165-170	166.5	30	69.5	37.0	5,900	3,200	4,573	26	10.4	27	35.2
170-175	171.8	47	69.3	38.8	5,750	3,150	4,415	40	13.1	41	35.5
175-180	177.0	24	69.4	42.0	5,650	2,800	4,306	21	13.4	21	35.6
180-185	182.2	24	69.7	34.7	6,300	3,500	4,548	19	9.7	19	35.5
185-190	186.3	21	69.8	35.6	6,250	3,200	4,807	19	12.0	18	35.9
190-195	191.4	22	69.2	40.4	5,400	2,900	4,245	24	13.8	24	35.7
195-200	196.1	18	71.0	34.6	6,950	3,050	4,485	15	9.2	15	36.2
200-205	201.3	16	69.3	41.5	5,350	2,900	4,169	13	14.5	13	35.6
205-210	206.4	11	69.8	37.5	5,700	3,500	4,341	9	10.6	9	36.4
210-215	210.9	11	71.2	42.0	5,650	3,500	4,450	10	14.2	10	37.0
215-220	216.8	14	70.3	35.6	5,650	3,300	4,543	11	11.8	12	36.5
220-225	221.7	9	71.2	37.8	5,500	4,000	4,672	5	16.1	5	36.9
225-230	226.0	9	71.3	41.9	6,150	3,300	4,194	8	15.1	9	36.4
230-235	232.6	5	69.3	36.2	5,750	2,800	4,440	4	11.0	4	36.3
235-240	237.3	3	70.8	44.3	5,200	3,850	4,417	3	15.3	3	36.9
240-245	240.0	2	72.1	36.5	4,700	4,525	4,613	2	11.0	2	35.8
245-250	249.0	1	71.0	44.0	4,650	4,650	4,650	1	24.0	1	37.0
250-255	250.0	1	73.0	34.0	5,600	5,600	5,600	1	12.5	1	37.0
255-260	.....	..	....	....	.....	.....	.....	..	....	..	....
260-265	264.0	1	73.5	54.0	5,550	5,550	5,550	1	12.0	1	37.0
265-270	.....	..	....	....	.....	.....	.....	..	....	..	....
270-275	.....	..	....	....	.....	.....	.....	..	....	..	....
275-280	.....	..	....	....	.....	.....	.....	..	....	..	....
280-285	280.0	1	73.5	29.0	4,700	4,700	4,700	1	9.0	1	39.0

TABLE 11.—*Observed and Calculated Vital Capacity of 418 Firemen Ranging in Body Weight from 125 to 285 Pounds (56.7 to 129.3 kg.)*

Body Weight, Pounds		Observed Mean Vital Capacity, C.c.	Calculated Vital Capacity, C.c.	Deviation of Calculated from Observed Values	
				Cubic Centimeters	Per Cent.
Range	Mean				
125-130	129.0	4,250	4,409	+ 159	+ 3.74
130-135	132.7	4,258	4,411	+ 153	+ 3.59
135-140	137.3	3,767	4,413	+ 646	+17.15
140-145	141.6	4,450	4,415	— 35	— 0.79
145-150	146.6	4,268	4,417	+ 149	+ 3.49
150-155	152.1	4,365	4,420	+ 55	+ 1.26
155-160	156.5	4,504	4,422	— 82	— 1.82
160-165	161.8	4,603	4,424	— 179	— 3.89
165-170	166.5	4,573	4,427	— 146	— 3.19
170-175	171.8	4,415	4,429	+ 14	+ 0.32
175-180	177.0	4,306	4,431	+ 125	+ 2.90
180-185	182.0	4,548	4,434	— 114	— 2.51
185-190	186.3	4,807	4,436	— 371	— 7.72
190-195	191.4	4,245	4,438	+ 193	+ 4.55
195-200	196.1	4,485	4,440	— 45	— 1.00
200-205	201.3	4,169	4,443	+ 274	+ 6.57
205-210	206.4	4,341	4,445	+ 104	+ 2.40
210-215	210.9	4,450	4,447	— 3	— 0.07
215-220	216.8	4,543	4,450	— 93	— 2.05
220-225	221.7	4,672	4,452	— 220	— 4.71
225-230	226.0	4,194	4,454	+ 260	+ 6.20
230-235	232.6	4,440	4,457	+ 17	+ 0.38
235-240	237.3	4,417	4,459	+ 42	+ 0.95
240-245	240.0	4,613	4,460	— 153	— 3.32
245-250	249.0	4,650	4,464	— 186	— 4.00
250-255	250.0	5,600	4,465	—1,135	—20.27
255-260	.....	.....	.....	.....	.....
260-265	264.0	5,550	4,471	— 79	— 1.42
265-270	.....	.....	.....	.....	.....
270-275	.....	.....	.....	.....	.....
275-280	.....	.....	.....	.....	.....
280-285	280.0	4,700	4,479	— 221	— 4.70

The range of variability as shown by the maximum and the minimum values (Table 10 and Chart 8) is very large, reaching about from one quarter to one half of the calculated values on each side of the central tendency curve.

The absolute and percentage deviations of the calculated from the observed averages are shown in Table 11. In only two of the averages are the percentage deviants more than 10 per cent., one average representing only one case and the other nine.

The weighted average deviants of the vital capacity-length of formula are recorded in Table 16. The weighted average absolute deviant is 1,403, and the weighted average percentage deviant, 3.19 per

TABLE 12.—*Changes in Calculated Vital Capacity of 418 Firemen Ranging in Body Weight from 120 to 280 Pounds (54.4 to 127 kg.)*

Body Weight, Pounds	Calculated Vital Capacity, C.c.	Increment		Percentage of Total Increment
		Cubic Centimeters	Percentage	
120	4,405.2	...	.....	.....
130	4,409.8	4.6	0.1044	6.25
140	4,414.4	4.6	0.1043	12.50
150	4,419.0	4.6	0.1042	18.75
160	4,423.6	4.6	0.1041	25.00
170	4,428.2	4.6	0.1040	31.25
180	4,432.8	4.6	0.1039	37.50
190	4,437.4	4.6	0.1038	43.75
200	4,442.0	4.6	0.1037	50.00
210	4,446.6	4.6	0.1036	56.25
220	4,451.2	4.6	0.1034	62.50
130	4,455.8	4.6	0.1033	68.75
240	4,460.4	4.6	0.1032	75.00
250	4,465.0	4.6	0.1031	81.25
260	4,469.6	4.6	0.1030	87.50
270	4,474.2	4.6	0.1029	93.75
280	4,478.8	4.6	0.1028	100.00

cent. This signifies that it is not possible to fit the formula of vital capacity-body weight quite as closely as in the case of body length, stem length or age. The relation is still within bounds of comparative accuracy, however, and the formula probably expresses a true though slight increase in vital capacity when it is related to body weight.

The percentage increment (Table 12) decreases almost impreceptibly because the absolute increment of body weight is only 4.6 c.c. per 10 pounds (4.5 kg.).

Twenty-five per cent. of the total increase in vital capacity between 120 and 280 pounds (54.4 and 127 kg.) of body weight has occurred at a body weight of 160 pounds (72.6 kg.), 50 per cent. at a weight of 200 pounds (90.7 kg.), and 75 per cent. at 240 pounds (108.8 kg.).

Vital Capacity in Relation to the Length of Service in the Fire Department.—Vital capacity steadily declines as the length of the service increases (Table 13 and Chart 9). The decrease in vital capacity in terms of years of service may be expressed by the empiric formula:

Vital capacity (cubic centimeters) = 4,840 — 34.84 times length of service (years).

The absolute vital capacity decreases steadily from 4,840 c.c. at the entrance to the fire department to 3,446 c.c. at the close of forty years of service, a decline of 174 c.c. every five years (Table 15).

TABLE 13.—*Observed Vital Capacity of 345 Firemen Ranging in Length of Service up to Forty Years*

Length of Service, Years		Number of Cases	Standing Height, Inches	Sitting Height, Inches	Age, Years	Body Weight, Pounds	Vital Capacity, C.c.		
Range	Mean						Maximum	Minimum	Mean
0- 1	0.3	1	71.8	35.5	22.0	150.0	4,400	4,400	4,400
1- 2	1.0	10	69.9	35.9	32.9	175.1	6,000	3,500	4,538
2- 3	2.2	5	69.4	34.7	32.0	174.8	5,750	4,100	4,560
3- 4	3.1	4	68.5	35.3	30.5	154.0	5,000	3,650	4,362
4- 5	4.4	70	69.1	35.6	29.1	173.7	6,950	3,200	4,602
5- 6	5.0	46	69.7	35.7	29.5	175.4	6,200	3,200	4,778
6- 7	6.0	6	70.2	36.0	31.0	184.5	5,200	3,050	4,425
7- 8	7.0	8	69.8	35.7	31.6	150.4	5,700	3,200	4,575
8- 9	8.0	11	69.9	35.6	31.5	179.2	5,500	4,050	4,564
9-10	9.0	17	70.4	35.8	32.2	188.2	5,800	3,600	4,762
10-11	10.0	9	68.6	35.1	38.3	176.9	5,200	3,250	4,106
11-12	11.0	13	69.7	36.3	36.9	187.2	6,150	3,750	4,592
12-13	12.1	16	69.1	35.1	37.6	182.8	5,600	3,300	4,602
13-14	13.0	11	70.0	35.9	41.5	177.5	5,400	2,900	4,223
14-15	14.0	13	68.6	35.1	41.6	171.4	5,200	3,000	4,173
15-16	15.0	7	70.2	35.9	42.9	189.1	5,400	3,700	4,500
16-17	16.0	8	69.8	36.2	45.3	194.0	5,100	2,900	4,119
17-18	17.0	7	69.1	35.3	48.0	167.8	5,650	3,200	4,143
18-19	18.1	8	69.2	35.4	44.5	182.5	5,300	3,150	4,238
19-20	19.1	9	68.4	35.1	49.7	170.5	4,450	3,200	3,789
20-21	20.0	9	70.8	36.0	48.2	193.6	5,550	3,400	4,567
21-22	21.0	4	68.7	35.8	46.2	185.5	4,600	3,650	4,150
22-23	22.2	7	70.4	35.7	51.9	183.0	4,800	3,600	4,119
23-24	23.0	3	68.1	35.3	49.0	183.0	3,800	3,150	3,483
24-25	24.0	4	68.9	35.5	56.0	190.8	4,650	2,900	3,912
25-26	25.0	1	67.5	32.0	55.0	148.0	4,475	4,475	4,475
26-27	26.0	2	68.4	35.1	50.5	207.5	3,650	3,300	3,475
27-28	27.0	4	69.1	35.8	57.0	179.0	4,400	4 050	4.225
28-29	28.0	6	68.7	35.1	57.0	188.5	4,400	3,500	3,767
29-30	29.0	6	69.5	35.6	53.0	167.3	4,900	3,250	3,900
30-31	30.0	6	68.8	34.5	55.7	184.8	4,800	2,800	3,958
31-32	31.0	4	69.9	35.2	59.3	181.0	5,000	2,900	3,750
32-33	32.0	2	68.2	35.4	55.5	170.5	4,250	3,900	4,075
33-34	33.0	1	67.3	36.0	59.0	177.0	2,900	2,900	2,900
34-35	34.0	1	63.3	33.5	61.0	139.0	3,500	3,500	3.500
35-36	35.0	2	67.4	34.8	57.5	173.0	3,900	3,850	3,875
36-37	....	..	....	....	....	.....	.....	.....	.....
37-38	37.0	1	64.5	33.0	61.0	133.0	4,000	4,000	4 000
38-39	38.0	1	70.7	23.8	63.0	186.0	3,600	3,600	3.600
39-40	39.0	2	71.5	35.4	62.5	191.0	4,150	3,600	3.875

As the length of service increases, so also does the age. In fact, the decline in vital capacity is undoubtedly due to the advancing age rather than to the length of service.

The body weight, body length and stem length remain practically the same throughout the entire length of service.

The range of variability, as shown by the maximum and the minimum values (Table 13 and Chart 10) varies between one third and one fourth of the calculated values on each side of the curve of central tendency.

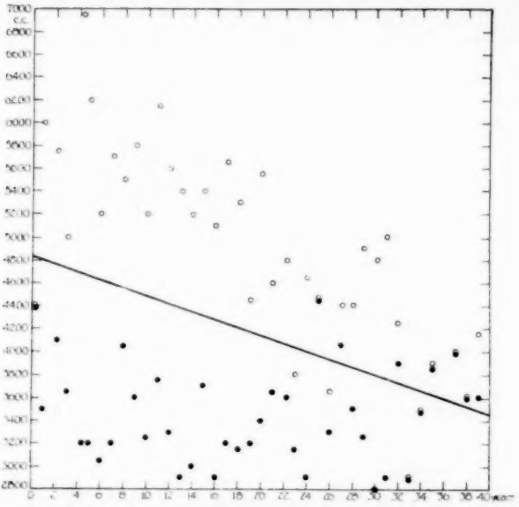

Fig. 10.—Relation between maximum and minimum vital capacity values and length of service in the fire department.

TABLE 14.—*Observed and Calculated Vital Capacity of 345 Firemen Ranging in Length of Service up to Forty Years*

Length of Service, Years		Observed Mean Vital Capacity,	Calculated Vital Capacity,	Deviation of Observed from Calculated Values	
Range	Mean	C.c.	C.c.	Cubic Centimeters	Per Cent.
0- 1	0.3	4,400	4,830	+430	+ 9.77
1- 2	1.0	4,538	4,805	+267	+ 5.88
2- 3	2.2	4,560	4,763	+203	+ 4.45
3- 4	3.1	4,362	4,732	+370	+ 8.48
4- 5	4.4	4,662	4,687	+ 25	+ 0.54
5- 6	5.0	4,778	4,666	—112	— 2.34
6- 7	6.0	4,425	4,631	+206	+ 4.66
7- 8	7.0	4,575	4,596	+ 21	+ 0.46
8- 9	8.0	4,564	4,561	— 3	— 0.07
9-10	9.0	4,762	4,526	—236	— 4.96
10-11	10.0	4,106	4,492	+386	+ 9.40
11-12	11.0	4,592	4,457	—135	— 2.94
12-13	12.1	4,602	4,418	—184	— 3.98
13-14	13.0	4,223	4,387	+164	+ 3.88
14-15	14.0	4,173	4,352	+179	+ 4.29
15-16	15.0	4,500	4,317	—183	— 4.07
16-17	16.0	4,119	4,283	+164	+ 3.98
17-18	17.0	4,143	4,248	+105	+ 2.53
18-19	18.1	4,238	4,209	— 29	— 0.68
19-20	19.1	3,789	4,175	+386	+10.19
20-21	20.0	4,567	4,143	—424	— 9.28
21-22	21.0	4,150	4,108	— 42	— 1.01
22-23	22.2	4,119	4,067	— 52	— 1.26
23-24	23.0	3,483	4,039	+556	+15.96
24-25	24.0	3,912	4,004	+ 92	+ 2.35
25-26	25.0	4,475	3,969	—506	—11.31
26-27	26.0	3,475	3,935	+460	+13.24
27-28	27.0	4,225	3,899	—326	— 7.72
28-29	28.0	3,767	3,864	+ 97	+ 2.58
29-30	29.0	3,900	3,830	— 70	— 1.79
30-31	30.0	3,958	3,795	—163	— 4.12
31-32	31.0	3,750	3,760	+ 10	+ 0.27
32-33	32.0	4,075	3,725	—350	— 8.59
33-34	33.0	2,900	3,690	+790	+27.24
34-35	34.0	3,500	3,655	+155	+ 4.43
35-36	35.0	3,875	3,621	—254	— 6.55
36-37	.....	.....	.....	.....	.....
37-38	37.0	4,000	3,551	—449	—11.23
38-39	38.0	3,600	3,516	— 84	— 2.33
39-40	39.0	3,875	3,481	—394	—10.17

The absolute and percentage deviations of the calculated from the observed values (Table 14) are quite evenly distributed. In seven of the average points, however, the percentage deviation is more than 10 per cent. Three of these averages represent only one case, two of them stand for only two cases, one for three, and one for nine.

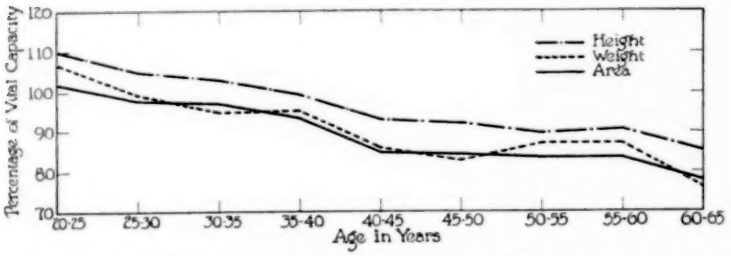

Fig. 11.—Vital capacity percentages obtained from formulas of Dreyer, West and others plotted against age.

The weighted average deviants of the vital capacity-length of service formula (Table 16) are larger than the deviants of the other vital capacity formulas already described. The weighted average absolute deviant is 150.2 and the weighted average percentage deviant, 3.52.

TABLE 15.—*Changes in Calculated Vital Capacity of 345 Firemen Ranging in Length of Service up to Forty Years*

Length of Service, Years	Calculated Vital Capacity, C.c.	Decrement		Percentage of Total Decrease
		Cubic Centimeters	Percentage	
0	4,840	.....	.....	.....
5	4,666	—174	—3.595	12.48
10	4,492	—174	—3.729	24.96
15	4,317	—175	—3.896	37.52
20	4,143	—174	—4.031	50.00
25	3,969	—174	—4.200	62.48
30	3,795	—174	—4.384	74.96
35	3,621	—174	—4.585	87.45
40	3,446	—175	—4.833	100.00

TABLE 16.—*Formulas of Vital Capacity with the Average Weighted Deviants (Y, Vital Capacity in Cubic Centimeters)*

X	Formulas	Average Weighted Deviants	
		Absolute, C.c.	Per Cent.
Standing height, inches	Y = 159.9X — 6,655	104.1	2.33
Sitting height, inches	Y = 218.9X — 3,290	112.8	2.53
Body weight, pounds	Y = 0.46X + 4,350	140.3	3.19
Age, years	Y = 5,725 — 34.46X	116.2	2.69
Length of service in fire department, years	Y = 4,840 — 34.84X	150.2	3.52

The percentage increment for five year intervals of service increases rather rapidly. Between 0 and 5 years, the increment is about 3.6 per cent., and, between 35 and 40, it becomes about 4.8 per cent.

Twenty-five per cent. of the total decrease in vital capacity during the thirty-nine years of service in the fire department is accomplished by the tenth year of service, 50 per cent. by the twentieth year and 75 per cent. by the thirtieth year.

After this study was made, it was decided to apply some normal standards already in use to our data. The standards used were the surface area standard of West, the standing height standard of West and the formula of Dreyer $\frac{\text{Wt.}^{0.72}}{\text{V.C.}} = 0.69$. Figure 11 shows that the curves prepared on the basis of surface area and Dreyer's formula very nearly coincide. This is in accordance with the findings of West, Myers and Cady and others. Indeed, it is to be expected since, in the formula of Dreyer, the surface area was duly considered. The curve prepared from the standing height standard shows that slightly higher percentages were obtained for the entire group when this standard was used. It is interesting to note that the Minneapolis firemen presented vital capacities well within normal limits by the surface area and Dreyer's formula until the age of 40 to 45 years was reached. After that age, they remained only slightly below normal limits until the age of 60 to 65 years was reached, when they dropped below 80 per cent. of the normal. When the standing height standard was employed, the average vital capacity was practically within normal limits until the age of 60 to 65 years.

PANCREATIC ENZYMES IN CHOLECYSTITIS*

GEORGE MORRIS PIERSOL, M.D.
AND
H. L. BOCKUS, M.D.
PHILADELPHIA

Cholecystitis is frequently associated with a certain degree of pancreatitis. Of 1,290 cases of diseases of the gallbladder and bile duct reported by Judd,[1] 347 or 26.8 per cent. had associated pancreatitis. In his cases, the clinical history did not, as a rule, suggest pancreatitis. The condition was determined at the time of operation by enlargement, hardening or edema of the pancreas. Deaver believes that cholecystitis causes a pancreatic lymphangitis, which condition precedes interstitial pancreatitis. Pancreatitis is sufficiently far advanced in over one fourth of the cases of gallbladder disease operated on to cause a macroscopic change in the organ. Another interesting illustration of the intimate relationship between gallbladder and pancreatic disease is the not infrequent occurrence of glycosuria in long standing cholecystitis.

In routine examination of the fasting duodenal juice for pancreatic enzymes, we frequently encountered an absence of, or a decrease in, the amount of one or more enzymes in cases of cholecystitis. It was decided to study the external secretion of the pancreas in a series of cases of proved cholecystitis, in order to ascertain whether the pancreatic involvement in cholecystitis is sufficient to cause a consistent reduction in the amount of enzyme present. The direct examination of the duodenal juice for pancreatic enzymes was first reported by Einhorn,[2] in 1910, following his discovery of the duodenal bucket, in January of the same year. This discovery opened up an entirely new field for investigation. It would seem that when pancreatic juice can be obtained directly for examination, a test based on such an examination should be the most reliable method available. The suprarenal mydriasis test of the Loewi, the iodobehenic test of Winternitz, the urinary diastase test and the Sahli capsule all have their advocates and all yield information of value to those familiar with their significance; but none of them alone is an absolute measure of pancreatic function.

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* From the gastro-intestinal clinic of the Graduate School of Medicine of the University of Pennsylvania.

1. Judd, E. S.: The Relation of the Liver and the Pancreas to Infection of the Gallbladder, J. A. M. A. **77**:197 (July 16) 1921.

2. Einhorn, Max: Experiences with Duodenal Contents, J. A. M. A. **55**, July 2, 1910.

METHOD

Einhorn [3] has devised an ingenious method of testing for pancreatic enzymes. It is patterned somewhat after the Mett tube method for pepsin determination, except that agar is used as a vehicle. The principle is that agar tubes in which albumin, starch and fat are mixed allow the ferment action to take place in them by osmosis. If the test substances are colored with indicators that undergo a change when acted on, it is easy to ascertain the presence of the ferments, and also to estimate their approximate amount by the volume of the tube change recorded in millimeters. When this study was first undertaken, several of the more complicated chemical methods were scrutinized and tried, but the method of Einhorn [4] was finally selected. It is undoubtedly the simplest method that can be considered at all reliable, and at the same time yields information as to the amount of enzyme present.

There is still a great deal to be desired so far as a method for accurately determining the amount of ferment is concerned. The basic principles of the chemistry of enzyme action are probably more nearly conformed to in the method recently described by McClure, Wetmore and Reynolds.[5] This method is too involved for routine clinical work and will probably never be universally adopted. The method selected is not alone responsible for the varied and conflicting results obtained. A frequent source of error is in the manner of collecting the duodenal juice for examination. There are extrapancreatic enzymotic substances selected for testing. Withdrawing chyme saturated with gastric juice from the duodenum, and subjecting it to examination for pancreatic enzymes, we believe to be a frequent source of confusion.

The fractional pancreatic analysis, as described by Einhorn, was done on eleven patients (Table 8). We feel that the information derived from the fractional method does not justify the additional two hours necessary to perform the test. It is possible to obtain the fasting duodenal juice, utilize it for pancreatic enzyme determination, and proceed with a Lyon-Meltzer bile drainage at one tubing. We agree with Friedenwald and Einhorn, that the fasting duodenal juice represents the highest point of enzyme concentration. At least, it represents the highest concentration level which can be obtained from a duodenum free from food and gastric juice. After a meal there is a drop in enzyme values, which gradually rise until the fasting figure is reached in about two hours. There is considerable fluctuation normally.

3. Einhorn, Max: M. Rec., Jan. 15, 1910.

4. Einhorn, Max: The Duodenal Tube, Philadelphia, W. B. Saunders Company, 1921.

5. McClure, C. W.; Wetmore, A. S., and Reynolds, L.: New Methods for Estimating Enzymatic Activities of the Duodenal Contents of Normal Man, Arch. Int. Med. **27**:706 (June) 1921.

Another factor which militates against the fractional method is that chyme is dumped into the duodenum at intervals, and it is impossible to tell what proportion of digestion is due to gastric juice and what amount is due to pancreatic enzymes.

METHOD OF OBTAINING SECRETION

The patient reports in the morning on a fasting stomach. The stomach is washed until clean and aspirated until dry, with the patient in the recumbent position. The tube is allowed to pass into the duodenum, the technic of Lyon being used. If there is free fluid in the duodenum, it is gently aspirated. If not, the tube is attached to a

TABLE 1.—*Normal Gall Tract*

No.	Age	Date	Diagnosis	Amylopsin	Trypsin	Steapsin
1	66	12/18/22	Normal	7	3	6
2	39	12/18/22	Normal	4.5	1.5	10.5
3	39	12/ 8/22	Normal	7	3	4
4	46	12/ 8/22	Normal	10.5	8.5	3.5
5	29	12/18/22	Normal	5	3	1
6	46	12/ 8/22	Normal	7	9.5	5.5
7	40	12/14/23	Achylia gastrica; indolic putrefaction	6.5	2.8	2.5
8	27	1/ 4/24	Spinal arthritis	4	9	10
9	39	8/16/22	Normal	20	3	2
10	38	2/13/24	Duodenal ulcer	5	3	1
11	37	2/16/24	Normal	0	7	5
		2/26/24		3.5	4.5	5
12	39	3/15/24	Achylia; syphilis	8.5	2	0.5
13	44	3/15/24	Duodenal ulcer	5	2	0.5
14	28	3/15/24	Gastric ulcer	6	1.5	1.5
15	39	3/19/24	Duodenal ulcer	6	0.5	0.5
16	16	3/19/24	Chronic appendicitis	0	0.5	0
17	44	3/25/24	Normal	9	2	0.5
		2/ 9/24		4	2	2
18	33	3/25/24	Normal	8.5	7	1
19	42	4/12/24	Achylia gastrica	11	8	10
		3/25/24		11	0	1.5
20	40	4/ 5/24	Stiller's disease	15	5	1
21	27	3/29/24	Normal	8	6	1.5
22	24	3/29/24	Catarrhal gastritis	10	4	1
23	60	3/29/24	Pyloric ulcer	8	2	5
24	31	.....	Normal	14	10	20
25	30	4/ 1/24	Duodenal ulcer	10	20	5
26	..	4/12/24	Normal	20	8	11
		Group average		8.3	5	3.5

bottle until about 10 c.c. of duodenal juice has been drained out. It is placed in a test tube and 1 drop of toluene is added to stop any bacterial activity. The Einhorn agar tubes, one each of starch, hemoglobin and olive oil, are dropped into the test tube after the end of the Einhorn tube covered with paraffin has been filed off. The test tube is placed in an incubator for twenty-four hours. Then it is removed, and the amount of digestion in each tube is measured in millimeters. The tubes must be freshly prepared each month and kept in the icebox. A tube in which the agar does not adhere to the capillary glass tube all the way down or one that has started to dry out should be discarded.

In Table 1 are grouped twenty-six patients whose gall tracts were normal. They were thoroughly studied from a gastro-intestinal stand-

point. The history, physical examination and the Meltzer-Lyon bile drainage yielded negative results in every case. A large proportion of them had negative roentgen-ray and fluoroscopic studies. Amylopsin varied from 0 to 20 mm.; seven patients had amylopsin reading of over 10 mm.; two patients had a reading of zero for the starch enzyme, but one of them at another time had 3.5 mm. for amylopsin. The other patient was a vagotonic boy who had chronic appendicitis. It is probable that the irritation of the tube set up a sympathetic vagus reflex, which caused a temporary suppression of pancreatic juice. In this case there was a complete absence of amylopsin and steapsin, and only 1.5 mm. of digestion in the hemoglobin tube. The average amount of amylopsin found in the fasting duodenal residium in this series of normal gall tract cases was 8.3 mm.

Friedenwald and Sindler[6] report a variation of from 1 to 15 mm. in amylopsin, in a series of normal cases. Their average amount of amylopsin, in normal cases, was 2.29 mm. Einhorn states that 6 mm. is the average amount of amylopsin found in normal cases. It is obvious that the starch enzyme is subject to very wide fluctuations, even in normal cases. Needless to say, a considerable source of error will be avoided if the same individual is assigned to make the readings. Amylopsin is the most variable of the pancreatic enzymes and the least reliable in computing pancreatic function.

Trypsin readings, in the normal group, varied from 0.5 to 20 mm. In only one case was more than 10 mm. of digestion found (the smaller range of fluctuation as compared with amylopsin should be noted); 5 mm. was the average amount of trypsin for this group. Friedenwald and Sindler's variation was from 1 to 12 mm., and their average for this enzyme was 5.8 mm.; Einhorn's normal average was 2.8 mm. The range of fluctuation is not nearly so great as with amylopsin, but it is still considerable.

The amount of steapsin in the normal group varied from 0 to 20 mm., but only three cases had a reading of over 10 mm. The average amount of steapsin present was 3.5 mm. Friedenwald and Sindler give from 1 to 12 mm. as their normal range of fluctuation, and 3.5 mm. as the average amount found. Einhorn's average for steapsin was 3.5 mm. Steapsin is the least variable of the enzymes and is probably the most important in the study of pancreatic dysfunction. It can be seen at a glance by consulting the first table that the strength of one enzyme is independent of the strength of the others. Friedenwald, Sindler and Einhorn are of the same opinion.

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6. Friedenwald, J., and Sindler, J.: Fractional Analysis of the Duodenal Contents in Normal Individuals, J. A. M. A. **177**:1469 (Nov. 5) 1921.

In recording the degree of fluctuation of enzymes, when more than one examination was made on a patient, the extreme figures were used. In computing the average amount of enzyme present in each series, if two or more examinations were made on one patient, the average amount

TABLE 2.—*Gallbladder Disease*

No.	Age	Date	Diagnosis	Duration of Symptoms, Years	Amylopsin	Trypsin	Steapsin
1	60	.....	Chronic cholecystitis	15	2.5	2	1
2	46	8/12/22	Chronic cholecystitis	10	7	3	4
		8/11/24		..	7	1	1
3	36	8/19/22	Subacute cholecystitis	2	2	2	...
4	35	8/15/22	Subacute cholecystitis	2	14	1.5	3
5	39	8/22/22	Cholelithiasis; operation	15	2	0	...
6	29	8/15/22	Chronic cholecystitis	1	7	7	3
7	36	2/11/24	Chronic cholecystitis; operation	9	2	1	7
8	28	12/ 4/23	Chronic cholecystitis	5	2	1.5	1.25
		12/ 7/23		..	5	3	0
9	44	12/ 8/23	Chronic cholecystitis; operation	8	0	1.5	1
10	41	12/ 8/23	Cholelithiasis; operation	5	5	6	6.5
11	43	12/18/23	Chronic cholecystitis	10	4	1	1
12	49	12/18/23	Cholelithiasis; operation	11	1.5	1	1
13	29	12/11/23	Chronic cholecystitis; duodenal ulcer	4	2	1	1
14	34	.....	Giardiasis; cholecystitis	10	5	5	3
15	25	1/ 8/24	Ankylostomiasis; chronic cholecystitis	3	8.5	2	0
16	24	1/15/24	Chronic cholecystitis; chronic appendicitis	2	0	5	1
17	30	2/ 5/24	Chronic cholecystitis	3	2	1	0
18	26	2/ 9/24	Giardiasis; chronic cholecystitis	3	3	0	4
		2/15/24		..	6	2	4
		3/11/24		..	2	1	7
19	74	.....	Chronic cholecystitis	30	0	1	5
20	43	2/ 9/24	Chronic cholecystitis; mucouscolitis	5	0	5	0
21	41	.....	Cholelithiasis; operation	10	1.5	1	1
22	33	2/ 9/24	Chronic cholecystitis	10	0	1.5	0.5
23	39	2/23/24	Chronic cholecystitis	7	7	1	0.5
24	40	2/26/24	Chronic cholecystitis	3	0	1	0
25	30	2/26/24	Chronic cholecystitis	2	0	1	0
		2/16/24		..	0	5	0
		3/15/24		..	2	2	0
26	48	2/26/24	Cholelithiasis	10	0	1	0
27	48	3/ 1/24	Cholelithiasis; operation	10	2	0	0
28	23	2/ 5/24	Chronic cholecystitis; chronic appendicitis	Under 2	9	12	2
		2/19/24		..	9	0.5	1
29	32	2/ 5/24	Chronic cholecystitis	4	0	0.5	0
		3/ 5/24		..	7	6	0
		3/29/24		..	8	1	1
30	32	2/ 5/24	Chronic cholecystitis	Over 5	1	1	0
31	42	2/ 5/24	Chronic cholecystitis	..	0	2	1
		3/11/24		..	3	1.5	1
32	44	2/ 5/24	Chronic cholecystitis; operation	10	5	2.5	3
		3/ 5/24		..	8	3	1.5
		3/11/24		..	0	0.5	0
33	36	3/19/24	Chronic cholecystitis; syphilis	6	10	1.5	1
34	25	3/20/24	Chronic cholecystitis	3	3	1	0
35	21	.....	Chronic cholecystitis	1	0	0.5	0
36	50	4/ 5/24	Chronic cholecystitis	20	7	1	0.5
37	46	3/21/24	Cholelithiasis	10	4	1	5
38	38	4/12/24	Cholelithiasis; operation	13	8	4	5
39	54	10/12/23	Chronic cholecystitis	10	0	0	0
		12/ 4/23		..	0	0	0
		4/ 5/24		..	0	0	0
40	57	.....	Chronic cholecystitis	5	5	2	2
		Group average			3.0	2.1	1.6

for each enzyme was computed and the resultant figure was used for that patient's normal, rather than the extreme figures. The most disappointing part of the normal group is the wide degree of fluctuation which occurs in the same patient when the pancreatic function is tested more than once under exactly the same conditions.

In Case 10, two examinations were made, ten days apart. There was a difference of 3.5 mm. of amylopsin and 2.5 mm. of trypsin, but the steapsin readings were identical. Two determinations were made on Case 17, six weeks apart. The difference in amylopsin was 5 mm.; in trypsin 1.5 mm., and in steapsin 1.5 mm. Two determinations were made on Case 19, three weeks apart. Amylopsin was the same, but a difference of 8 mm. was present in the two readings for trypsin, and a discrepancy of 8.5 mm. in the steapsin readings. This emphasizes again the great variability even in the same individual and under like conditions. In a doubtful case, more than one determination should be done and a careful feces analysis made. Whipple [7] studied a series

TABLE 3.—*Variation in Quantity of Enzyme*

	Extremes in Amount of Amylopsin	Extremes in Amount of Trypsin	Extremes in Amount of Steapsin
Gall tract normal group, Table 1	0 to 20 7 cases over 10	0.5 to 20 1 case over 10	0 to 20 2 cases over 10
Gallbladder disease group, Table 2	0 to 11 1 case over 10	0 to 12 1 case over 10	0 to 7

TABLE 4.—*Relation Between Duration of Symptoms and Amount of Enzyme Present in Cholecystitis*

Duration of Symptoms	Average Amount of Amylopsin	Average Amount of Trypsin	Average Amount of Steapsin	Number of Cases
Ten years or more	3.2	1.5	1.8	16
From 5 to 9 years	3.3	2.1	1.8	11
From 2 to 4 years	2.9	1.8	1.1	11
Under 2 years	5.3	4.5	1.5	3

of cases for pancreatic ferments before operation and concluded that the interpretation of decreased activity in any one or more of three enzymes is difficult, and suggests checking any questionable case with a stool examination. He believes that gross changes at operation are not necessarily an indication of functional disturbance of the pancreas.

GALLBLADDER DISEASE

Forty cases of gallbladder disease were studied in the manner outlined above. The diagnosis was confirmed by operation in nine cases. The roentgen-ray studies indicated a pathologic gallbladder in nine other cases. In the remaining twenty-two cases, the diagnosis was made by the usual diagnostic procedures, history, physical examination and the Lyon-Meltzer drainage method. These cases will be found in Table 2. There was a variation in the starch enzyme in this group

7. Whipple, A. O.: Use of the Duodenal Tube in Preoperative Study of the Bacteriology and Pathology of the Biliary Tract and Pancreas, Ann. Surg. **73**:556 (May) 1921.

of from 0 to 14 mm. In only one case was the reading over 10 mm. The proteolytic enzyme varied from 0 to 12 mm., with only one reading over 10 mm. Steapsin varied from 0 to 7 mm. By consulting Table 3, it will be seen that the range of fluctuation is distinctly less in the cholecystitis cases. This is more noticeable in the fat splitting enzyme, which did not rise above 7 mm. This marked reduction in the amount of fat splitting enzyme in cholecystitis may be more of a factor in the causation of poor fat digestion than is generally believed. The incomplete handling of fats in cholecystitis has usually been considered to be caused by a disturbance of the mechanism at the ampulla of Vater resulting in an insufficient quantity of bile being poured out into the intestines during the digestive phase.

TABLE 5.—*Cholelithiasis*

No.	Age	Date	Diagnosis	Duration of Symptoms, Years	Amylopsin	Trypsin	Steapsin
1	39	8/22/22	Operation	15	2	2	...
2	41	12/ 8/23	Operation	5	5	6	6.5
3	49	12/18/23	Operation	11	1.5	1	1
4	41	.....	Operation	10	1.5	1	1
5	48	2/26/24	.....	10	0	1	0
6	48	3/ 1/24	Operation	10	2	0	0
7	38	4/12/24	Operation	13	8	4	5
8	46	3/21/24	.....	10	4	1	5
Group average					3	2	2.6

TABLE 6.—*Disease of the Pancreas and Liver, Not Cholecystitis*

No.	Age	Date	Diagnosis	Amylopsin	Trypsin	Steapsin
1	31	1/29/24	Diabetes	0	0	0
2	..	1/21/24	Diabetes	5	1	1.5
3	26	1/29/24	Arsphenamin jaundice	8.5	2	3
4	36	2/19/24	Arsphenamin jaundice	3.5	1	2
5	29	2/26/24	Arsphenamin jaundice	5.5	4.5	3
6	46	1/ 8/24	Intestinal cancer; metastasis to liver	0	1.5	4
7	46	2/19/24	Myocarditis; cirrhosis of liver; ascites	2	2	3

A further study of Table 2 reveals a persistent absence of all enzymes in one case, and a persistent absence of two enzymes in three cases. Trypsin was absent from the fasting duodenal juice in three instances. Amylopsin was absent in eleven cases and steapsin in ten cases. In the cholecystitis cases in which the enzymes are considerably below normal, there is less fluctuation in the amount of enzyme from day to day. The fat splitting enzyme varies less when more than one determination is made on one patient.

The average amount of amylopsin present in the series of forty cases of gallbladder disease was 3.6 mm., as compared with 8.3 mm. in the normal group (Table 7). The average amount of trypsin was 2.1 mm., as compared with 5.0 in the normal group. The group average for steapsin was 1.8 mm., as compared with 3.5 mm. in the normal group.

Of the series of forty cases of cholecystitis, seventeen cases, or 42.5 per cent., had all three enzymes reduced in amount more than 50 per cent.; eleven cases, or 27.5 per cent., had a reduction of over 50 per cent. in two enzymes, and six cases, or 15 per cent., had a reduction of over 50 per cent. in one enzyme. Eighty-five per cent. of the cases studied having a gallbladder pathologic condition had a reduction of over 50 per cent. in one or more enzymes. In making this computation, when more than one determination was made on the same individual, the highest reading was used and not the average reading for that patient.

Dowden and Enfield,[8] using the method described by Whipple, concluded that the pancreatic enzyme determination was too variable to be reliable. The method used was not a quantitative one. An analysis of their cases shows that of twenty-seven cases of gall tract disease, 25 per cent. had a complete absence of trypsin, and 14 per cent. had no steapsin; whereas in twenty-five cases in which there was no gall

TABLE 7.—*Group Averages*

Diagnosis	Number of Cases	Amylopsin	Trypsin	Steapsin
Gall tract normal, Table 1	26	8.3	5	3.5
Gallbladder disease, Table 2	40	3.6	2.1	1.6
Cholelithiasis, Table 5	8	3	2	2.6
Diabetes, Table 6	2	2.5	0.5	0.7
Arsphenamin jaundice, Table 6	3	5.8	2.5	2.7

tract pathologic conditions, amylopsin was absent in five cases, trypsin in one, and steapsin in six cases.

In order to determine what relation existed between duration of disease and degree of reduction of enzymes, the cases of cholecystitis were subdivided into four groups (Table 4). In the few cases in which the duration of symptoms was under two years, the amount of enzyme present was practically the same as the average for the normal group. There seemed to be little difference, however, between the amount of enzyme present in the patients having symptoms between two and four years and those having symptoms over ten years.

CHOLELITHIASIS

Eight of the patients included in Table 2 had gallstones. They have been classified separately in Table 5 to ascertain if there was a greater reduction in the stone cases. The average amounts of amylopsin (3 mm.) and trypsin (2 mm.) are slightly below the amounts of those enzymes in the general cholecystitis group. The steapsin average is slightly above that of the cholecystitis group (Table 7). Although the

8. Dowden, C. W., and Enfield, C. D.: The Duodenal Tube in the Study of Liver and Pancreatic Pathology, South. M. J. **15**:103 (Feb.) 1922.

number of cases is too small to base conclusions, there seems to be little difference between cholelithiasis and cholecystitis in their effect on the external secretion of the pancreas.

Two cases of diabetes were studied (Table 6). All three enzymes were absent in one case, and in the other there was a marked reduction in the amount of trypsin and steapsin.

Three cases of arsphenamin jaundice show an average slight reduction in all three enzymes.

TABLE 8.—*Fractional Pancreatic Analysis*

Case	Enzymes	Fasting	½ Hour after Food	1 Hour after Food	1½ Hours after Food	2 Hours after Food
1. Gall tract normal.....	Amylopsin.....	0	5	9	10	8
	Trypsin.....	2	1	4	3	5
	Steapsin.....	0.5	0.5	1.5	0.5	0.5
2. Chronic cholecystitis...	Amylopsin.....	7	2	7	0.5	4
	Trypsin.....	1	4	2.5	1	1
	Steapsin.....	1	1	1	0	1
3. Chronic cholecystitis...	Amylopsin.....	2.5	3	3	3	4.5
	Trypsin.....	2	0.5	2.5	1.5	2
	Steapsin	1	0.5	1.5	1	0.2
4. Chronic cholecystitis...	Amylopsin.....	2	2	0	1.5	2
	Trypsin.....	2	1	0	0.5	1
	Steapsin.....	...	...	...	...	...
5. Chronic cholecystitis...	Amylopsin.....	5	2	4	5	5
	Trypsin.....	1	1.5	3	2	2
	Steapsin.....	4	0.5	0.5	4	4
6. Chronic cholecystitis...	Amylopsin.....	3	4	2.5	6	6
	Trypsin.....	1.5	2	3	3	2
	Steapsin.....	1	1	0	1.5	2
7. Chronic cholecystitis...	Amylopsin.....	5	8	0	2	4
	Trypsin.....	2.5	3	0.5	1	1
	Steapsin.....	2	1.5	0	0.5	0.5
8. Chronic cholecystitis...	Amylopsin.....	0	0	2	4	4
	Trypsin.....	0.5	0.5	0.5	0.5	0.5
	Steapsin.....	0	0	0	0.5	0.5
9. Chronic cholecystitis...	Amylopsin.....	8	10	6	7	...
	Trypsin.....	4	9	8	8	...
	Steapsin.....	5	15	10	0	...
10. Diabetes.....	Amylopsin.....	0	6.5	7	12.5	8
	Trypsin.....	0	1	3	2	2
	Steapsin.....	0	0	0	3.5	1
11. Normal.....	Amylopsin.....	2.5	4	6	3	3
	Trypsin.....	1	1.5	1.5	1	2.5
	Steapsin.....	...	...	...	...	...

SUMMARY

1. A series of twenty-six cases having normal gall tracts were studied by the Einhorn agar tube method for pancreatic enzymes, using the fasting duodenal juice for the determination.

2. The fractional pancreatic analysis has a greater source of error and is more time consuming.

3. There is considerable range of variation in all of the enzymes, even in the same individual. Amylopsin is the most variable and the least stable. Trypsin and steapsin are almost on a par as to degree of variability, steapsin probably varying less. In patients having normal

gall tracts and without disease of the pancreas, we found the average amount of enzymes to be: amylopsin, 8.3 mm.; trypsin, 5.0 mm., and steapsin, 3.5 mm.

4. Forty cases of cholecystitis were studied in a similar manner. The range of fluctuation in the amount of enzyme was found to be greatly reduced in gallbladder disease. This was particularly true of steapsin.

5. A considerable number of cases of gall tract disease had one or more enzymes absent.

6. The average amount of each enzyme in cholecystitis was reduced to more than 50 per cent. of the normal amounts.

7. Eighty-five per cent. of all cases of gallbladder disease studied had a reduction of over 50 per cent. in the amount of one or more of the enzymes.

8. The fat splitting enzyme was more consistently reduced in amount. Trypsin was a close second.

9. A few cases of gallbladder disease presenting symptoms for less than two years had no appreciable reduction in the amount of enzymes. After two years, the duration of symptoms bears no relation to the degree of reduction of enzymes.

10. Eight cases of cholelithiasis showed an average reduction below normal in the quantity of enzymes corresponding closely to the reduction in the general cholecystitis cases.

CONCLUSIONS

Testing the duodenal secretion for pancreatic enzymes has been generally considered of little value, owing to the extensive range of fluctuation which is usually encountered. When the secretion of an organ can be obtained for examination, such an examination should yield information of value as to the function of that organ. However, no absolutely reliable clinical method has been devised for testing the functional capacity of the pancreas, particularly that part of the pancreas concerned with enzyme production.

By using a simple quantitative method, probably as accurate as any so far devised, we have found a marked reduction in the amount of the pancreatic enzymes in 85 per cent. of forty cases of cholecystitis. We feel that this method of examination, when carefully performed, yields information of value concerning the function of the pancreas. A definite reduction in the amount of the pancreatic enzymes in a doubtful case of cholecystitis is additional corroborative evidence in favor of that malady, just as achylia gastrica should suggest the presence of gallbladder disease until the latter can be definitely ruled out.

THE DEMONSTRATION OF TRANSIENT JAUNDICE IN GALLSTONE COLIC*

E. MEULENGRACHT, M.D.
COPENHAGEN, DENMARK

It is difficult to say how often the symptom jaundice occurs in gallstone patients. It is a symptom which the patients and their associates take remarkably little notice of, or the statements are so vague that nothing can be made of them. It is also difficult to ascertain how frequently jaundice follows the attacks themselves, and any data will be vitiated if we do not clearly define what we mean by an attack and what we mean by jaundice. If we take an attack to mean a severe attack and jaundice to mean even the slightest sign of the symptom, the frequency of occurrence will be relatively great, and vice versa. I contend that the symptom will occur more often and its diagnostic value, therefore, will be increased by a systematic search for it, that is to say, by looking for it at times when there is a likelihood of its being present and by looking not only for manifest jaundice but also for occult jaundice, by examining for bile pigment in the blood and urobilin in the urine. By thus searching for this symptom, we can derive considerable help in the diagnosis of gallstones from its presence, although I shall show that jaundice is, of course, by no means a sine qua non in the diagnosis of the disease.

I shall begin by discussing the investigation for bile pigment in the blood, and then deal with the examination for urobilinuria—the two methods of investigation which are appropriate for the demonstration of the slight, the doubtful, or the entirely occult forms of jaundice.

The reason for examining the blood for bile pigment is that the increase of bile pigment in the plasma must reach a certain value before it becomes actually visible as jaundice of the skin and sclerotics, and before it is excreted in the urine in quantities that can be detected. The necessary increase in the plasma varies in the different forms of jaundice. It is usually greater in jaundice of a hemolytic nature and smallest in pure obstructive jaundice. But it also depends on the duration of the jaundice which is clearly evident in the case of the urine, for in acute jaundice excretion of bile pigment in the urine more readily takes place while in more chronic cases it is more firmly combined in the plasma and is not so easily excreted. It appears to be a general rule that the bile pigment is present in greater concentration in the plasma than in the tissues and urine in generalized jaundice. As regards the urine, I shall illustrate this point with some examples given in Table 1.

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*From the Medical Department B, Bispebjerg Hospital.

The amount of bile pigment in the plasma was determined by the dilution method, which I have previously described,[1] the principle of which is that by diluting the plasma until it matches a standard tint we measure how yellow it is. The method is useful and convenient. Values up to 5 are within normal limits; above 5 they represent a pathologic increase.

It will be seen from Table 1 that the different forms of jaundice have high plasma color values, and that if, in the same manner, we measure approximately how yellow the urine is,[2] we find that, even in cases of most complete obstructive jaundice, the urine is always lighter in color than the plasma, so that other laws are operative in the case of the bile pigment than apply, for example, to sugar, for we measure the blood sugar in parts per thousand but the urine sugar in parts per cent.

TABLE 1.—*Presence of Bile Pigment*

	Plasma	Urine	Rosenbach Test
Hemolytic jaundice	32	< 5	±
Hemolytic jaundice	54	< 5	±
Hemolytic jaundice	41	< 5	±
Pernicious anemia	21	< 5	±
Catarrhal jaundice	44	30	+
Catarrhal jaundice	30	< 5	±
Catarrhal jaundice	180	27*	±
	700	390	+
Hepatic cirrhosis	26	15	?
Carcinoma of pancreas	190	180	++
Carcinoma of pancreas	84	45	++
Carcinoma of pancreas (?); stone in common bile duct	250	55	++
Carcinoma of stomach; metastases in liver	130	100	++
Carcinoma of stomach; metastases in liver	76	60	++

* On one day the urine was light in color, and on the other it was dark.

1. An account of the method is given in the Deutsch. Arch. f. klin. Med. **132**, Parts 5 and 6, 1920; ibid. **137**, Parts 1 and 2, 1921. It is best to use the ready made apparatus (Meulengracht's Bilirubin Colorimeter, manufactured by Paul Altmann, Berlin N.W. 6. Louisenstrasse 47). It resembles the Sahli hemoglobinometer with two glass tubes and a ground glass plate. One of the tubes contains the faintly yellowish standard solution and serves as a comparison; the other is graduated and is used for the dilution. If the tint of the colorimeter is not good (too greenish) one can prepare a standard tube for oneself with the standard liquid: potassium bichromate, 0.05; distilled water, 500; sulphuric acid, 2 drops. The technic is as follows: About 3 c.c. of blood are taken with a dry, sterile cannula from the arm vein into a small test tube in which 2 drops of 3 per cent. sodium oxalate solution have been previously put to prevent coagulation. The tube is inverted a few times and placed in a stand for from twelve to twenty-four hours until the blood corpuscles have sedimented; or, if one is in a hurry, it can be centrifugated. With the pipet, 0.5 c.c. of the supernatant plasma is transferred to the tube graduated in two and one-half cubic centimeters. It is then diluted with physiologic sodium chlorid solution till it matches the color of the solution in the standard tube. The height of the liquid measured by the graduations of the tube gives the "plasma color value," "bilirubin value" or "jaundice index." If the value is greater than 15, the plasma must be diluted beforehand and the value obtained multiplied by the degree of dilution.

2. It is only a very rough estimation as the color of the urine is not determined by the bile pigment (bilirubin) alone.

When, therefore, one advocates determinations of bile pigment in the plasma in the diagnosis of gallstones, it is because the very slight degrees of jaundice are not visible or are doubtful in the skin and cannot be detected by the excretion of bile pigment in the urine, and, furthermore, the remains of jaundice which is disappearing can be most easily recognized, or only recognized, in this way.

It is true that the acute obstructive jaundice which occurs in connection with gallstones is one of the forms of jaundice in which bile pigment is most readily excreted in the urine.[3] But that plasma determinations are useful in spite of this I can show with the help of some examples.

TABLE 2.—*Observations in Case 1*

C. O., a woman, aged 56; April 24 to Sept. 16, 1922; morbus cordis, cholelithiasis; had previously had similar attacks; while in the hospital for heart disease, a typical gallstone attack occurred.

	Visible	Plasma	Rosenbach Test	Urobilin	
August 27. Pain, vomiting					
August 28	+	32	+	++ } Trace }	Temperature raised
August 29	+	28	Trace	++ Trace	
August 30	?	..	+	++ Trace	
August 31	?	7	+	++ Trace	
September 1	+	..	+	+ +	
September 2	+	6	+	+ +	
September 3	+	..	+	+ +	
September 4	+	4	+	+ +	
September 5	+	..	+	+ +	
September 6	+	3–4	+	+ +	

There was typical tenderness. The feces had no stones and were not clay colored.

If, as a first example, we look at Table 2, we see how an attack with clearly visible jaundice progresses. Jaundice is only present temporarily for a few days after the attack of pain. The plasma color values are increased; bile pigment is excreted in the urine (Rosenbach's test), and there is urobilinuria (Schlesinger's method as well as Marcussen's and

3. In my first publication (Deutsch. Arch. f. klin. Med. **132,** 1920) on bile pigment in the blood, I spoke of a "threshold" for skin jaundice and a "threshold" for the excretion of bile pigment in the urine. I wrote that these boundaries were extremely different in the various forms of jaundice, which is a fact. In the case of the skin and sclerotics, they are commonly about 8, 10, 12 or 15. In the case of the urine, I gave too high values at that time as I had usually investigated chronic forms of jaundice. Subsequently, I have observed that in acute gallstone attacks the excretion of bile pigment may occur in the urine with a plasma color value below 10.

S. Hansen's modification in a dilution 1:10). The tests for plasma and urobilin are here superfluous as the jaundice is directly visible.

In Table 3, we see a typical example of the necessity of examining the plasma and testing for urobilinuria in order to catch the rapidly disappearing jaundice. Nothing was seen in the skin. Rosenbach's reaction in the urine was doubtful.

I may perhaps venture to say that all these reactions (Gmelin's, Rosenbach's and Trousseau's) for bile pigments in the urine are, on the whole, always bad and ambiguous except in the more marked forms of jaundice. One investigator will return a positive result and another

TABLE 3.—*Observations in Case 2*

A. M., a woman, aged 36, June 7 to June 20, 1922; cholelithiasis, achylia gastrica; had had attacks for five years; had always been treated for achylia, had been admitted with this diagnosis. She had had a severe attack on the day before admission.

	Visible	Plasma	Rosenbach Test	Urobilin
June 8	÷	12	Trace	++++ +++
June 9	÷	5	÷	++ +
June 10	÷	4	÷	+ ÷
June 11	..	..	..	÷ ÷
June 12	..	..	..	÷ ÷
June 13	÷	3	÷	÷ ÷
June 14	..	..	..	÷ ÷
June 18	..	..	..	..
June 19	÷	3	÷	÷ ÷

There was typical tenderness; no stones were present in the feces, and they were not clay colored. Operation was done June 28; a number of stones were found in the gallbladder and the cystic duct.

a negative result, and we resort to a glance at the patient in order to decide by the presence or absence of jaundice whether to call the reaction positive or negative.

Table 4 shows quite a similar case. There is doubtful jaundice of the sclerotics, as is often the case, so that one is undecided about it. On examining the plasma, a numerical value is obtained, and it is concluded that there has been brief transient jaundice in connection with the pain.

Table 5 shows that it is, of course, not necessary to make a series of investigations but that we may confine ourselves to carrying out a plasma determination and a test for urobilinuria after an attack of pain and then repeat the tests some days later. In private practice, it will often happen that benefit can be derived from the tests in the consulting room; there has been an attack of pain, and the investigation shows that it has been accompanied by transient occult jaundice.

TABLE 4.—*Observations in Case 3*

J. L., a man, aged 45; August 5 to 14, 1922; cholelithiasis; had never had a previous attack; admitted for abdominal colic; pain began four days before admission; particularly severe pain on admission.

	Visible	Plasma	Rosenbach Test	Urobilin	
August 5. Pain	?	10	÷	..	Temperature slightly raised
August 6. Pain	?	13	÷	++ +	
August 7	÷	6	÷	++ +	
August 8	÷	..	÷	++ +	
August 9	÷	3	÷	+ ÷	
August 10	÷	..	÷	÷ ÷	
August 14	÷	3	÷	÷ ÷	

There was slight tenderness; the feces were not clay colored; no stones were present. Subsequently, the patient passed a stone at home.

TABLE 5.—*Observations in Case 4*

A. J., a woman, aged 31, May 11 to 22, 1921; cholelithiasis; had been treated for some time for gastric disease; four days before admission, had had an attack in the right side, back and shoulder blades, associated with vomiting; had had pain now and again since; admitted for cholelithiasis.

	Visible	Plasma	Rosenbach Test	Urobilin	
May 12	÷	11	?	+++ +	?Temperature raised
May 13	..	..	..	..	
May 14	..	..	..	..	
May 15	..	..	..	..	
May 16	..	..	..	..	
May 17	÷	2	÷	÷ ÷	

There was typical tenderness.

TABLE 6.—*Observations in Case 5*

E. P., a woman, aged 24, April 13 to 23, 1921; cholelithiasis; had had a previous attack; four or five days before admission had an attack of pain with vomiting; was admitted for cholelithiasis.

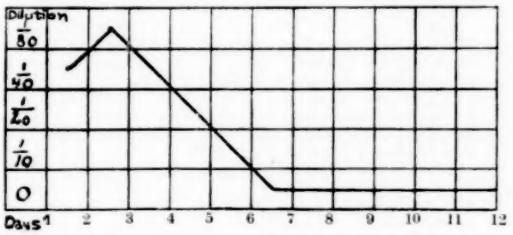
	Visible	Plasma	Rosenbach Test	Urobilin
April 14	÷	7	÷	+++ ++
April 15	÷	..	..	..
April 16	÷	4	÷	Trace ÷

There was tenderness in the epigastrium; the temperature was normal.

It is not advisable to give general rules for the standard to be set up for recognizing occult jaundice. Sometimes, one will be inclined to be satisfied with little, as, for instance, in Table 6, when there is reason to believe that one has to deal with the last traces of jaundice, which has been more pronounced on the preceding days but is now disappearing.

From the examples cited, it will be seen how the slight jaundice has been continuously accompanied by urobilinuria. Thanks to S. Hansen's article [4] on urobilinuria in cholelithiasis, it is now generally known that, in the transient urobilinuria following an attack, we possess an excellent aid to diagnosis in cholelithiasis.

In the accompanying chart, I have reproduced the type curve which S. Hansen found. He also found urobilinuria with extraordinary regularity after an attack; after twenty-three attacks (comparison should be made with the chart) he discovered an increased excretion of



Urobilinuria in Cholelithiasis (S. Hansen)

Urobilin reaction.....	1/20—1/80	1/10	0
Thirty-three attacks.....	29	4	0

urobilin in the urine in all cases. He concludes, therefore, that the symptom is "almost constant" after a gallstone attack.[5] I have, however, been unable to observe such a constancy of the symptom, and I can only explain S. Hansen's constant finding as the result of chance, or as an indication that he has been particularly strict with regard to what he will recognize as a gallstone attack, and especially lax with regard to what he will allow to be a positive urobilin reaction, since there is a definite subjective factor involved in adjudicating on them. I shall give some examples below of the absence of urobilinuria in undoubted attacks accompanied by slight manifest jaundice or a small increase in the plasma color values (Tables 7 and 8).

I must, therefore, state that genuine attacks may occur without the association of any of the elements of jaundice whatever (Tables 9 and 10).

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4. Hansen, S.: Ugesk. f. Laeger. **82**:415 (March 25) 1920.

5. Cases of stone in the common bile duct with total shutting off of the intestine are excluded.

TABLE 7.—*Observations in Case 6*

E. P., a woman, aged 55, Nov. 27 to Dec. 17, 1921; cholelithiasis, obesity; had had a series of attacks at home, described as heart attacks; was admitted for heart disease and obesity; had had attacks for the last two days before admission.

	Visible	Plasma	Rosenbach Test	Urobilin	
November 27	+	37	+	+	
				+	
November 28	+	..	+	+	
				+	
November 29	+	15	+	+	Temperature slightly raised
				+	
November 30	Trace	6	+	+	
				+	
December 1	+	7	+	+	
				+	
December 2	+	7	+	+	
				+	
December 3	+	..	+	+	
				+	
December 4	+	5	+	+	
				+	
December 5	+	..	+	+	
				+	
December 6	+	5	+	+	
				+	

There was no tenderness; no stones were present in the feces, and they were not clay colored.

TABLE 8.—*Observations in Case 7*

J. L., a woman, aged 32; Nov. 26, 1919 to Jan. 21, 1920; cholelithiasis; for a year the disease was regarded as colitis; had had attacks of pain; was admitted for colitis.

	Visible	Plasma	Rosenbach Test	Urobilin
December 14. Attack of pain				
December 15. Attack of pain				
December 16	Trace	16	+	+
				+
December 17	+	..	+	+
				+
December 18	+	6	+	+
				+
December 19	+	..	+	+
				+
December 20	+	5	+	+
				+
December 21	+	..	+	+
				+
December 22	+	5	+	+
				+
December 23	+	..	+	+
				+
December 28	+	4	+	+
				+
January 5	+	4	+	+
				+

There was fairly typical tenderness; the temperature was normal. An operation was performed January 21. A number of stones the size of hemp seeds were found in the gallbladder.

To recapitulate my opinion of the diagnostic value of jaundice in cholelithiasis, I consider that its value is considerably enhanced if the slight or occult degrees are searched for. It will then appear that a considerably larger proportion of the cases than is generally believed are accompanied by slight transient jaundice. But there are, of course, two points on which we must be clear. In the first place, jaundice can mean much more than cholelithiasis. Just as we may be deceived by manifest jaundice into diagnosing cholelithiasis, we may also be led astray by the slighter degrees of jaundice if we hunt for them assiduously and attribute too great diagnostic importance to them. Thus, like

TABLE 9.—*Observations in Case 8*

E. J., a woman, aged 33; Oct. 4 to 13, 1921; cholelithiasis; had had attacks for ten years, which were diagnosed as gastric disease; was admitted for hepatic colic.

	Plasma	Urobilin
October 6	5	±
		+
October 7. Pain	..	±
		±
October 8. Severe attack	..	±
		±
October 9. Pain	5	±
		+
October 10	..	..
October 11	3	±
		+
October 12	5	+
		±
October 13	4	±
		+
October 14	..	+
		+
October 15	4	±
		+
October 16. Severe attack	4	±
		+
October 17. Pain	..	..
October 18. Pain	5	±
		+

There had been typical severe attacks, with typical tenderness each time. No stones were in the feces. The temperature was normal. An operation was performed, October 31; two stones the size of a cherry were found in the gallbladder.

others, I have been led on a false scent. The same applies here as to albuminuria which, although it may signify many different things, is nevertheless a valuable aid to diagnosis in nephritis. It should, therefore, only be kept in mind that jaundice, manifest or occult, may also signify other things, such as disease of the liver cells, or it may be of an infectious nature. But what is characteristic of a gallstone attack is that transient jaundice of short duration occurs in conjunction with pain which clinically resembles gallstone colic.

What might at first be expected to cause difficulty is transient jaundice and transient urobilinuria of an infectious nature, that is to say, caused by toxic bacterial action on the liver cells. For this to happen,

however, higher fever or special infections must usually be present, so that these difficulties will not, as a rule, be great in the clinic.

Secondly, as I have mentioned, we must realize that gallstone colic need not be accompanied by jaundice in any of its manifestations (Tables 9 and 10).

When jaundice is manifest, one is spared further investigation and, as a rule, in practical diagnosis one is glad to avoid it as much as possible. But, if it is a question of looking for occult jaundice, it may be asked which of the two methods of investigation is to be preferred, the examination for bile pigment in the plasma or the examination for urobilinuria. Theoretically, the two investigations supplement each other and the urobilinuria may be absent while the other symptom is present. In a well appointed department where skilled assistance is

TABLE 10.—*Observations in Case 9*

A. A., a woman, aged 33; May 26 to June 20, 1922; cholelithiasis, achylia gastrica; had had attacks for three years; was admitted for cholelithiasis (?).

	Visible	Plasma	Rosenbach Test	Urobilin	
June 9. Severe attack	÷	3	÷	÷	
				÷	
June 10	÷	3	÷	..	
June 11. Severe attack	÷	3	÷	..	
June 12	÷	..	..	..	
June 13	÷	..	..	..	
June 14. Severe attack	÷	3	÷	÷	
				÷	
June 15	÷	3	÷	÷	
				÷	
June 16	÷	..	..	++	Temperature 38-39 C.
				+	
June 17	÷	..	..	++	
				+	
June 18	÷	3	÷	÷	
				÷	
June 19	÷	..	..	..	

The gallbladder was palpable. No stones were in the feces. There was typical tenderness. Operation was done July 3; two stones were found in the gallbladder, one firmly impacted in the cystic duct.

forthcoming, it may perhaps be a matter of indifference which of the methods is employed or whether both of them are made use of. But in private practice it is otherwise.

The diagnosis cholelithiasis is one which, to a great extent, is made in the home in actual practice, and one cannot, in this case, as in other diseases, leisurely subject the patient to various examinations and so make the diagnosis by steps, but one must strike while the iron is hot and make the diagnosis when the patient has an attack. Whether it is tenderness or jaundice that is searched for, we must seize the opportunity while it is there. Thus, it is of no avail to make use of too complicated apparatus and methods for the demonstration of jaundice which waste time. In this respect, each of the two methods has its advantages and disadvantages. In the examination for urobilinuria,

venipuncture is avoided; this, however, should not entail any difficulties. The examination by Schlesinger's method [6] will, as a rule, be adequate when it is only a question of a strong reaction and when it is remembered that the reagent is somewhat altered on keeping. Marcussen and S. Hansen's modification [7] in a dilution 1:10 is likewise fairly simple and rapid. But a disadvantage in a urobilin determination is that a twenty-four hours' sample of urine should really be used because individual samples may vary considerably, partly on account of the changing diuresis and partly on account of variations in the twenty-four hours' excretion.[8] I myself consider that the plasma determination is convenient and well adapted for the consultation room. It seems to me that, in the consultation room, it is simpler to take a sample of blood than obtain a twenty-four hours' sample of urine, and, with practice, it is only necessary to let the tube with the oxalated blood stand till the blood corpuscles have sedimented. It is then possible to see directly whether the plasma is yellower than it ought to be, and it is unnecessary to obtain the actual numerical value.[9]

The chief point, if it is desired to make use of jaundice as the basis of differential diagnosis, is to select the right time, as already pointed out; and the mode of procedure must therefore be to instruct the patient, in doubtful cases in which there is a suspicion that he is suffering from gallstones, to present himself or send for the doctor when there has been an attack of pain, so as to afford one the opportunity of investigating whether jaundice in any of its manifestations occurs in direct association with such an attack.

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6. Schlesinger's method: Equal parts of urine and the vigorously shaken reagent (zinc acetate 10, absolute alcohol 90) are mixed and left to stand for twenty-four hours. Above the flocculent precipitate, there is a column of clear liquid. A green fluorescence in the latter denotes the presence of urobilin. If it is desired to read the result immediately, two or three drops of tincture of iodin (1:20) must be mixed with 10 c.c. of urine and then filtered. (On the addition of iodin the urobilinogen present is oxidized to urobilin; on standing this takes place spontaneously.) The reading is taken by reflected ordinary daylight, preferably against a dark background. As an excess of zinc is essential, the reagent must be vigorously shaken especially because the zinc acetate powder is transformed into a coarse crystalline mass difficult to disperse, on keeping. Ammoniacal urine should be overneutralized with acetic acid.

7. Marcussen and S. Hansen's modification (Ugesk. f. Laeger **80**:16 [Jan. 3] 1918): 1 c.c. urine and 4 c.c. distilled water and 2 drops of tincture of iodin are mixed together; 5 c.c. of the reagent (zinc acetate 2, absolute alcohol 100) are added. It is then shaken. The result is read after filtration or on standing.

8. Weltmann, Oscar; and Tenschert, Otto: Ueber die Tagesschwankungen im Urobilinogengehalt des Harnes bei Gesunden und Kranken, Wien. med. Wchnschr. **18**:766-770, 1922.

9. Hijmans von der Bergh's method for the demonstration of bile pigment in the blood which is now employed extensively is, in my opinion, much too complicated for the present purpose, and it is also subject to large quantitative errors (my paper in the Deutsch. Arch. f. klin. Med. **137**, 1921).

THE AGE CURVE OF PULSE RATE UNDER BASAL CONDITIONS *

W. D. SUTLIFF, M.D., AND EVELYN HOLT, M.D.
NEW YORK

This study was undertaken with the following ends in view:

1. To furnish standards, so far as the available data will permit, of the average normal pulse rate under basal conditions and the extent of normal variations from this average.

2. To observe the changes in pulse rate with age and with sex.

3. To compare the age curve of pulse rate with the age curve of metabolic rate.

Data have been obtained through a survey of the published records of basal metabolism experiments, in which normal subjects were studied.

REVIEW OF THE LITERATURE

It is not our purpose to present a complete review of the literature on the subject of pulse frequency. The reader is referred to the work of Tigerstedt [1] for a thorough discussion. Only a few points which appear pertinent to the subject matter of this study will be mentioned.

Average normal values given by Tigerstedt are copied from tables given first by Volkmann,[2] and based on data collected by Volkmann, Guy [3] and Nitsch,[4] separately. The conditions while not basal were uniform, in that the rates were taken with the subject sitting in a chair, resting, and from two to four hours after the last meal. A number of these average values at various ages are given in Table 1. It will be noted that Volkmann did not give separate values for the two sexes. The general trend of pulse frequency with age according to this table may be summarized as follows: highest in infancy, 134 at 1 year, it drops rapidly at first, reaching 111 at 2 years, then drops more gradually to ninety at 9 and 10 years, seventy-four at 20 years, then remains constant until 55 and rises slightly in old age. These values compare closely with what MacKenzie [5] offers: at birth from 130 to 140, ninety

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* From the Second Medical (Cornell) Division of Bellevue Hospital, and the Department of Medicine, Cornell University Medical College.

1. Tigerstedt, R.: Die Physiologie des Kreislaufes, Ed. 2, Berlin and Leipzig, de Gruyter, 1921, pp. 429-472.

2. Volkmann, A. W.: Die Haemodynamik, Leipzig, 1850, pp. 407-445.

3. Guy, W. A.: The Pulse, in Todd, R. B.: Cyclopaedia of Anatomy and Physiology **4**:181-194, 1847-1849.

4. Nitsch, quoted from Tavastzerna, A.: Zur Kenntnis der Individuellen Schwankungen des Blutdruckes beim gesunden Menschen, Skand. Arch. f. Physiol. **21**:405-430, 1909.

5. MacKenzie, James: Diseases of the Heart, Oxford Med. Pub., 1908, pp. 120-135.

at 9 or 10 years, seventy-four at 20 years, from 66 to 76 at from 30 to 50 years with some increase after 50 years. Many other authorities agree closely with Volkmann, showing that his work has been the usual source of statements regarding the normal pulse rate, and that it appears to be confirmed by the findings of clinicians in everyday practice.

Variations within normal limits have been indicated in Volkmann's table by giving the highest and lowest observation at each age, together with the number of observations. There are differences of from 40 to 60 beats per minute, roughly from 20 to 30 per cent. above and below the average, slightly greater in youth than in adult life and old age.

TABLE 1.—*Comparison of Pulse Rate at Different Ages Under Different Standard Conditions*

Age	Men and Women Not Basal from Volkmann	Men—Basal		Women—Basal	
		Benedict et al.	Bailey	Benedict et al.	Bailey
1	134	116	...	122	...
2	111	104	...	103	...
3	108	92	...	86	...
4	108	...	100	87	99
5	103	...	91	91	88
6	98	87	97	80	97
7	93	85	92	73	92
8	94	80	100	77	101
9	89	81	93	85	100
10	91	79	84	80	92
11	87	75	84	...	92
12	89	69	90	80	89
13	88	76	87	82	86
14	87	75	83	79	81
15	82	70	77	77	82
16	83	71	77	77	83
17	80	68	74	72	78
18	76	...	76	73	78
19	77	65	77	71	78
20	74	64	73	69	74
20–40	71	62	75	68	77
40–60	73	57	70	70	74
60–70	74	66	66	71	78
70 and over	75	65	...	73	...

Sex was clearly shown by Guy [3] to produce a difference in pulse rate. At every age after 2 years the females of his series have a more rapid rate than the males, the difference being slight up to 7 years, after that from 6 to 14 beats per minute with an average of 9 beats per minute. Friberger [6] gives a table of the average pulse rate of boys and of girls from 6 to 15 years of age, in which the difference in the sexes averages 11 beats per minute. Volkmann,[2] on the other hand, showed that when women and men of the same body length were compared, there was no constant difference. He ascribes the difference noted by Guy and others to body size and draws analogies from the animal kingdom, large animals having slower, small animals having faster pulse rates. The validity of these arguments has been somewhat

6. Friberger, R.: Ueber die Entwicklung von Puls und Blutdruck in späteren Kindesalters, Arch. f. Kinderh. **60**:331-339, 1913.

lessened by more recent work. Benedict [7] has used the biometrical method of correlation coefficients, to find what relationship stature and pulse rate may have to one another and states: "As far as available data justify conclusions concerning the problem, they seem to indicate that there is only a very slight if any interdependence between stature and minimum or basal pulse rate in man."

Age, it appears, plays a definite part in the differences in pulse frequency. Volkmann showed that persons of the same size, but younger, have more rapid pulses.

Tigerstedt [1] considers the variety and number of factors which influence the pulse rate in normal persons. Muscular exertion is the principal one. All manner of external stimuli, even internal stimuli such as produced by body processes or emotions have immediate and marked effect. In commenting on the data of Volkmann, Guy and Nitsch, he says that had the subjects been at more nearly perfect rest the average values would be lower. He quotes several observers on the effect of rest on the pulse rate. Aulo [8] showed that there was a gradual fall of the pulse rate during rest to a level reached after from eighty to one hundred minutes. At what appeared to be complete rest, with a curve the average point of which remained constant at about 50 beats per minute, variations continued to occur from minute to minute as great as 10 per cent. above and below the average. We find no other data which indicate the occurrence of variations as great as those noted by Aulo. Bleuler and Lehmann [9] counted the pulse of a subject every five or ten minutes, from 8:25 a. m. to 8:12 p. m., and found that the rate varied from 59 to 64, about 5 per cent. above and below the average. It is a common experience in basal metabolism work to find variations of from 1 to 5 beats per minute in repeated counts after the patient has rested for thirty minutes. This would indicate that Aulo's subjects were extraordinary in the variability of their pulse rates, or that the resting conditions were not so complete as those which are required in basal metabolism determinations. Aulo showed that the fall in pulse rate during sleep was approximately the same in amount as that at complete rest, but that during sleep the fall occurred more quickly. Klewitz [10] states that during the day there is no difference in the pulse of subjects asleep and the pulse of subjects awake and at rest, but that at

7. Harris, J. A., and Benedict, F. G.: A Biometric Study of Basal Metabolism in Man, Publication 279, Carnegie Institute, 1919.

8. Aulo, T. A.: Zur Kenntnis der Pulsfrequenz des Menschen bei Muskelruhe und im Schlaf, Skand. Arch. f. Physiol. **21**:266-276, 1909.

9. Bleuler, E., and Lehmann, K. B.: Ueber einige wenig beachtete wichtige Einflusse auf die Pulszahl des gesunden Menschen, Arch. f. Hyg. **3**:215-248, 1885.

10. Klewitz, F.: Der Puls im Schlaf, Deutsch. Arch. f. klin. Med. **112**: 38-55, 1913.

night during sleep a greater fall occurs. Korösy [11] made the observation that a group of soldiers between the ages of 20 and 24 had an average pulse rate of 63.3. These men were resting quietly in bed in the morning. A short interval was allowed to elapse after they were wakened and no food was given. The conditions may be considered basal. He calls attention to the fact that the average is lower than that obtained by Volkmann,[2] Guy,[3] Nitsch,[4] Quetelet,[12] Vierordt [13] and others whose conditions were not basal.

In recent years, the workers on metabolism have collected a large amount of data on the pulse frequency under basal conditions. In basal metabolism work, the observations are made with the subject in the postabsorptive and resting state, the fall in pulse rate to a constant level being one of the criteria of the length of rest required. The largest amount of this work has been done by Benedict [14] and his co-workers of the Nutrition Laboratory of the Carnegie Institution of Washington. Detailed discussions of the basal pulse rate may be found in the publications of the Carnegie Institution dealing with infants, older children and adults.

Infants studied by Benedict and Talbot [14] during the first 5 days of life showed a slight progressive decrease during the first 3 days, then a return to the original or a slightly higher level. The rates showed a marked drop from the fetal average of 135 beats per minute to an average of 112 beats per minute the first day after birth. The fetal pulse was studied first by Kegaradec,[15] whose original observations have been confirmed by many different workers. Naegele,[16] in 600 observations, finds the extremes to range from 90 to 180, with an average of from 130 to 140. Premature infants have been studied by Talbot, Sisson and Moriarty.[17] The infants were estimated to be from forty-three to 108 days premature. Pulse rates ranged from 110 to 185 with an average of 140 to 150, much faster than those of either the fetus or new-born children.

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11. Korösy, K.: Studien über Puls und Atmunsgsfrequenz, Deutsch. Arch. f. klin. Med. **101**:267-282, 1911.

12. Quetelet, A.: Anthropométrie, Bruxelles, 1870, pp. 370-374.

13. Vierordt, H.: Anatomische, Physiologische, und Physikalische Daten und Tabellen, Ed. 3, Fischer, Jena, 1906, pp. 230-237.

14. Benedict, F. G., and Talbot, F. B.: The Physiology of the New-Born Infant, Pub. 233, Carnegie Inst., 1915. Benedict, F. G., and Talbot, F. B.: Metabolism from Birth to Puberty, Pub. 302, Carnegie Inst., 1921. Harris, J. A., and Benedict, F. G.: A Biometric Study of Basal Metabolism in Man, Pub. 279, Carnegie Inst., 1919.

15. Kegaradec: Mémoire sur l'auscultation appliquée à l'étude de la grossesse, Paris, 1822 (quoted in Williams' Obstetrics, Ed. 5, 1923, p. 207).

16. Naegele, O. V.: Die geburtshilfliche Auscultation, Mainz, 1838, p. 35 (also in Preyer: Die spezielle Physiologie des Embryo, 1885, p. 43).

17. Talbot, Fritz B.; Sisson, Warren R., and Moriarty, Margaret E.: Basal Metabolism of Prematurity, Am. J. Dis. Child. **26**:29-55 (July) 1923.

During the first year of life pulse rates appeared from the work of Benedict and Talbot [14] to remain approximately the same. A definite trend downward is observed to begin in most of the individual subjects at any point from the fourth to the fourteenth month. In all it appeared before the eighteenth month.

The decrease in childhood is shown by averages selected by Benedict and Talbot.[14]

TABLE 2.—*Decrease of Pulse Rate in Childhood (Benedict)*

Age	Pulse Rate	Age	Pulse Rate
1	121	7	78
2	100	8	78
3	89	9	82
4	87	10	81
5	91	12	72

The drop shows many irregularities, as at 5 years and 9 and 10 years, differing in this respect from the uniform curve produced by the data of Volkmann,[2] Guy,[3] and Nitsch.[4]

The effect of sex on the pulse rate is definitely shown in Benedict and Talbot's observations on children only in those under 1 year of age. Girls have higher rates from 1½ to 10 months. There is a tendency to a higher rate in girls than boys in the data from 1 year to puberty; however, fifteen of twenty-six age periods show girls higher while eleven show boys higher. Benedict and Talbot [14] say: "On the whole, the picture cannot be said to speak for a higher pulse rate with girls than with boys."

In adults, the grand averages of Harris and Benedict's [7] cases show a marked difference between the sexes. One hundred and twenty men averaged 61.26 beats per minute, while ninety women averaged 68.87 beats per minute. These figures are remarkably constant in the different sections of the large groups done at separate times and places and by different men. This indicates an average difference in adult men and women of 7.6 beats per minute with sex.

Other men have studied the pulse under basal conditions. Addis,[18] working with soldiers aged from 21 to 23, under basal conditions finds an average of 63 beats per minute and under conditions not basal an average of 80 beats per minute. He shows the variability of the pulse under basal conditions by the odds against the appearance in his series of a given rate higher than the average. For instance, Addis says that the chances that a rate of 88 is normal are only 1 in 1,000. Peterson and Walter [19] summarize 2,500 basal observations on 1,200 clinic

18. Addis, T.: Blood Pressure and Pulse Rate Levels, Arch. Int. Med. **29**:539-553 (April) 1922.

19. Peterson, Anne; and Walter, Will: Basal Metabolism and Ideal Weight and Pulse Ratios, J. A. M. A. **78**:341-343 (Feb. 4) 1922.

patients, and find the average for men 66, for women 74. These may be compared to the clinic patients observed by Bailey, mentioned later. In regard to variations Peterson and Walter state that a rate of over 82 in men or over 90 in women is cause for suspicion of hyperthyroidism.

The relation between pulse and age has been taken up by Harris and Benedict [7] in addition to the data given in the foregoing on changes in childhood. The method of correlation coefficients was used on the data of the Nutrition Laboratory for adults: 120 men ranging from 16 to 67 years, but mainly between 20 and 35, and ninety women ranging from 15 to 74, but mainly between 20 and 30. They found that there was a slight negative correlation, indicating a decrease in pulse rate with advancing age, in this age group. Harris and Benedict [7] say in regard to this: "The amount of change is so small that its nature has not been investigated." They quote Whiting's correlations of the same factors, pulse and age, using data gathered by Goring on prisoners, but not under basal conditions. His results indicate a positive correlation, an increase with age. Benedict suggests that without basal conditions and possibly the presence of increased lability of the pulse with age, these contradictory findings of Whiting may be explained.

The investigation of the relationship of the technic and apparatus concerned in the taking of basal metabolism measurements to the results obtained, has yielded some interesting observations on the effect of mixtures rich in oxygen on the pulse rate. Benedict and Higgins [20] found a slight, but perceptible fall in rate with the use of air mixtures for breathing, containing 60 per cent. oxygen, and a definite drop of about 4 beats per minute when 80 per cent. oxygen was used. Parkinson,[21] and Schneider and Sisco,[22] also observed a drop in pulse rate, but only with the use of high percentages of oxygen. Since the oxygen, even in the closed circuit apparatus of the recent portable type almost never rises to 60 per cent., interference with any of the observations used in this study is not likely.

Metabolism and pulse rate have been studied for possible relationship by a number of men. Murlin and Greer [23] showed that pulse rate has less relation to oxygen absorption than the product used to express total heart action, pulse pressure multiplied by pulse rate.

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20. Benedict, F. G., and Higgins, H. L.: Effects on Men at Rest of Breathing Oxygen-Rich Gas Mixtures, Am. J. Physiol. **28**:1-18, 1911.

21. Parkinson, John: The Effect of the Inhalation of Oxygen on the Rate of the Pulse in Health, J. Physiol. **44**:54-58, 1912.

22. Schneider, E. C., and Sisco, D. L.: The Circulation of the Blood in Man at High Altitudes, Am. J. Physiol. **34**:1-47, 1914.

23. Murlin, J. R., and Greer, J. R.: The Relation of Heart Action to the Respiratory Mechanism, Am. J. Physiol. **33**:253-282, 1914.

Benedict and Cathcart [24] showed that pulse rate and heat production are not proportional in greater muscular activity. Murlin and Hoobler [25] state that under the same conditions in the same person, minor fluctuations in muscular activity are accompanied by minor fluctuations in pulse rate and basal metabolic rate, but that at different ages in the same infant, this does not hold true. A certain infant, sleeping, showed a pulse of 140, at the age of 2 months, and a pulse of 112 at the age of 12 months, while the heat production at the latter age amounted to twice that of the earlier age. Harris and Benedict [7] cite the fact that women have a higher pulse rate than men and at the same time a lower metabolic rate as indicating that "the average pulse rate may have little if any connection with average heat production in a group of individuals." Benedict and Talbot,[14] by an elaborate series of kymographic observations of infants' movements taken during the periods of metabolism experiments, were able to observe that the metabolism varies closely with the movements and pulse rate varies closely with both. The record of the pulse rate proved a better practical guide to the changes in metabolism than the record of movements. They conclude that in a given infant, variations of pulse rate do accompany variations in metabolism. Sturgis,[26] in observations of one patient with hyperthyroidism through 192 consecutive days, observed that the resting pulse rate indicated the changes which occurred in the metabolism with few exceptions. It appears to be the general opinion among metabolism workers who study hyperthyroid cases, that when the relation of pulse rate to metabolic rate is once learned in a given case, changes in metabolism may be noted with a fair degree of certainty at a subsequent time (Means and Aub,[27] and others). In different persons the relationship of pulse to basal metabolism is not comparable, however. From a consideration of the opinions of these authors there seems to be no true relationship between basal pulse rate and basal metabolic rate, except in the individual.

On the other hand, Harris and Benedict,[7] again using correlation coefficients, with the data of the adult series before mentioned, find a slight positive correlation between pulse rate and total heat production. The degree of correlation is increased by the use of calories per square meter of body surface, thus correcting for the differences in the size of

24. Benedict, F. G., and Cathcart, E. P.: Muscular Work, Pub. 187, Carnegie Inst., 1913.

25. Murlin, J. R., and Hoobler, R. B.: The Energy Metabolism of Ten Hospital Children, Am. J. Dis. Child. **9**:81-119 (Feb.) 1915.

26. Sturgis, Cyrus C.: Observations on One Hundred and Ninety-Two Consecutive Days of Basal Metabolism, Food Intake, Pulse Rate, and Body Weight in a Patient with Exophthalmic Goiter, Arch. Int. Med. **32**:50-73 (July) 1923.

27. Means, J. H., and Aub, J. C.: Basal Metabolism in Exophthalmic Goiter, Arch. Int. Med. **24**:645 (Dec.) 1919.

the subjects. Since the correlation is positive in sign it indicates that pulse rate is higher with higher metabolic rates and vice versa in adults. Read [28] has also used the method of correlation coefficients with the factors, pulse pressure, pulse rate and basal metabolic rate in a series of 300 observations in thyroid patients and thyroid suspects. He found a high correlation of both pulse rate and pulse pressure with metabolic rate, and with the resulting formula he calculated the metabolic rate in his own series of cases from observed pulse pressure and pulse rate within 10 per cent. of the actual value found in 60 per cent. of the cases and within 20 per cent. in 91 per cent. of the cases. This tends to show that in thyroid states at least the pulse rate and pulse pressure have a considerable and fairly constant relation to basal metabolism.

This review of the literature in regard to pulse rates under basal conditions indicates that there is a use and a need for standards of average normal values. Hobson,[29] writing in 1923, says: "No absolute values can be attached to the observations (pulse) since we have nothing but the crudest guides as to the normal pulse rate." Sturgis and Tompkins,[30] on finding in three hyperthyroid patients, after treatments, but with normal metabolism, pulse rates of 57, 55 and 52, considered these abnormally low. It will be shown in the data given below that pulse rates of this order are not infrequent.

SOURCE OF MATERIAL

Unfortunately, we could not base our data on a sufficient number of personal observations, and therefore it is necessary to give the sources from which we gathered material. The work of Benedict and his associates in Boston is particularly valuable, as the purpose of this work was to study normal persons under basal conditions. Practically all of the figures on infants, and many of those on adult men and women come from this source. The subjects were all chosen as normal controls, and were studied in the postabsorptive state, at least twelve hours after the last meal, lying quietly after a rest of at least half an hour. The exception to this is the infants, who were studied immediately after a feeding for the reason that they were quiet at no other time, and quiet is more important than the effect of food. One very interesting set of observations, the studies of the girl scouts, we did not consider comparable with the other work and were forced to omit. These groups of twelve girls occupied a large respiration cham-

28. Read, J. M.: Correlation of Basal Metabolic Rate with Pulse Rate and Pulse Pressure, J. A. M. A. **78**:1887-1889 (June 17) 1922.

29. Hobson, F. G.: A Comparative Study of Basal Metabolism in Normal Men, Quart. J. Med. **16**:363-389 (July) 1923.

30. Sturgis, Cyrus C., and Tompkins, Edna H.: A Study of the Correlation of the Basal Metabolism and Pulse Rate in Patients with Hyperthyroidism, Arch. Int. Med. **26**:467-476 (Oct.) 1920.

ber for the night. The girls were warned to be quiet in the morning and the pulse was counted twice before they got up or had breakfast.[31] The conditions as regards rest and food were basal, but the two counts show such wide variations as to indicate that, in spite of the advice as to quiet, there was probably a large factor of excitement. In a second series [32] the pulse was counted during sleep, giving figures which probably represent the minimal pulse rate, but which are hardly comparable with counts made while the subject is awake. Other figures were obtained from the studies of normal persons made by Magnus-Levy and Falk [33] (who studied basal metabolism using the Geppert-Zuntz method as described in Pfluger's Archives), by Palmer, Means, and Gamble,[34] by Blunt and Dye,[35] and by Hobson [29] (working with the Benedict apparatus), and by DuBois [36] and his associates in their studies with the Sage calorimeter. These workers all describe their methods in detail, and no figures were used unless it seemed quite clear that the conditions were basal and the subjects normal. Exception has been taken to the conditions under which DuBois studied the boy scouts. These were unusually vigorous boys, who came into the city from the suburbs, and who had a small breakfast at 6:30 or 7:00 a. m., three or four hours before the experimental period. Soderstrom, Barr and DuBois have shown that such a breakfast does not affect the metabolism after two or three hours, and DuBois states that the

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31. Benedict, F. G., and Hendry, M. F.: The Energy Requirements of Girls from 12 to 17 Years of Age, Boston M. & S. J. **184**:217-230, 257-262, 282-286, 297-306, 329-334, 1921.

32. Benedict, F. G.: The Basal Metabolism of Young Girls, Boston M. & S. J. **188**:127-138 (Feb. 1) 1923.

33. Magnus-Levy, A.: Ueber Aufgaben und Bedeutung von Respirationsversuchen für die Pathologie des Stoffwechsels, Ztschr. f. klin. Med. **33**:258-268, 1897; Untersuchungen zur Schilddrüsenfrage, Ztschr. f. klin. Med. **33**:269-314, 1897. Magnus-Levy, A., and Falk, E.: Der Lungengaswechsel des Menschen in den verschiedened Alterstufen, Arch. f. Physiol., 1899, supplement, pp. 314-367.

34. Palmer, W. W.; Means, J. H., and Gamble, J. L.: Basal Metabolism and Creatinin Elimination, J. Biol. Chem. **19**:239-244, 1914.

35. Blunt, K., and Dye, M.: Basal Metabolism of Normal Women, J. Biol. Chem. **47**:69-87 (June) 1921.

36. Gephart, F. C., and DuBois, E. F.: The Determination of the Basal Metabolism of Normal Men and the Effects of Food, Arch. Int. Med. **15**:835-867 (May) 1915. Soderstrom, G. F.; Meyer, A. L., and DuBois, E. F.: A Comparison of the Metabolism of Men Flat in Bed and Sitting in a Steamer Chair, Arch. Int. Med. **17**:872-886 (June) 1916. DuBois, E. F.: The Metabolism of Boys Twelve and Thirteen Years Old Compared with the Metabolism at Other Ages, Arch. Int. Med. **17**:887-901 (June) 1916. Gephart, F. C., and DuBois, E. F.: The Basal Metabolism of Normal Adults with Special Reference to the Surface Area, Arch. Int. Med. **17**:902-914 (June) 1916. Aub, J. C., and DuBois, E. F.: The Basal Metabolism of Old Men, Arch. Int. Med. **19**: 823-831 (May) 1917. Soderstrom, G. F.; Barr, D. P., and DuBois, E. F.: The Effect of a Small Breakfast on Heat Production, Arch. Int. Med. **21**:613-620 (May) 1918. Olmstead, W. H.; Barr, D. P., and DuBois, E. F.: Metabolism of Boys Twelve and Fourteen Years Old, Arch. Int. Med. **21**:621 (May) 1918.

boys were quiet, being allowed to read for part of the experimental period. Benedict,[14] while he does not criticize the breakfast allowed the boys, states that in the first series muscle activity caused such great irregularities in metabolism (sometimes a difference of 12 per cent. in successive hours) that the conditions cannot be considered basal. He accepts the experimental conditions of the second series.

By some of the observers the pulse was counted with a stethoscope, while by others it was counted at the wrist. Theoretically, in every case the count should be made without the subject's knowledge; practically, with careful work, it seems to make little difference. In examining the records the relative constancy of the basal pulse rate from minute to minute is very striking. In fact, when there are marked variations, one suspects that the conditions were not truly basal.

PRESENTATION OF DATA

In assembling our data we have tried to show the findings by a series of charts constructed to show the pulse rates observed for each year, both in males and in females. These charts are constructed on the same scale, using years as abscissas, in each case the age being taken as that of the nearest birthday,[37] and pulse rates as ordinates. The base line is placed at 40 because a pulse of 0 is impossible and because it is said that a pulse of less than 40 should arouse a suspicion of heart block.[38] Each observation is put down with a symbol to indicate the observer, and a line is drawn to show the general average. This line is drawn by inspection, not showing the actual arithmetic average for each year, these averages being given in Table 1, but attempting to indicate the general trend. We believe that this is a fair procedure and one which shows the situation more accurately than if we gave the sharp up and down variations as they appear from year to year. There is no reason to believe that these zigzag variations actually occur, and were the series of cases larger, they would doubtless disappear as in Volkmann's [2] series. As we shall try to make clear in the comment the position of the line in puberty and in old age is open to question. We have drawn the line tentatively on the basis of present information, realizing that it is open to revision when more adequate reports are available.

Table 1 compares the average pulse rate, not basal, for a large series of normal persons, male and female, with the basal pulse rates of normal controls and of objectively healthy clinic patients. The first series is taken from Volkmann;[2] the figures for the normal controls under basal

37. An exception was made in the case of one man and two women over 80. Here the age was considered to be 80.

38. Lewis, Thomas: Clinical Disorders of the Heart Beat, Ed. 5, New York, Paul B. Hoeber, 1921, p. 5.

conditions are the averages of the observations shown in the charts; while the basal pulse rates of clinic patients were obtained through Dr. C. V. Bailey, of the Post-Graduate Hospital.

Charts 1 and 2 show the pulse rates of males between the ages of 1 and 80, with the average drawn in as explained in the foregoing. Certain points are evident on inspection of the chart, namely, the rapid

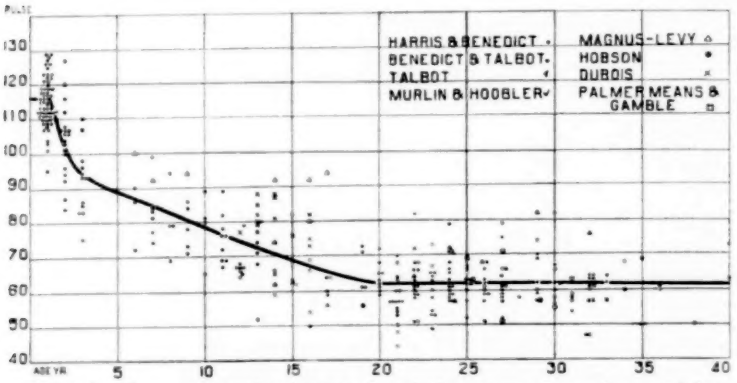

Chart 1.—Curve of basal pulse rate in relation to age for males, aged from 1 to 40 years. Source of the data is indicated by symbols.

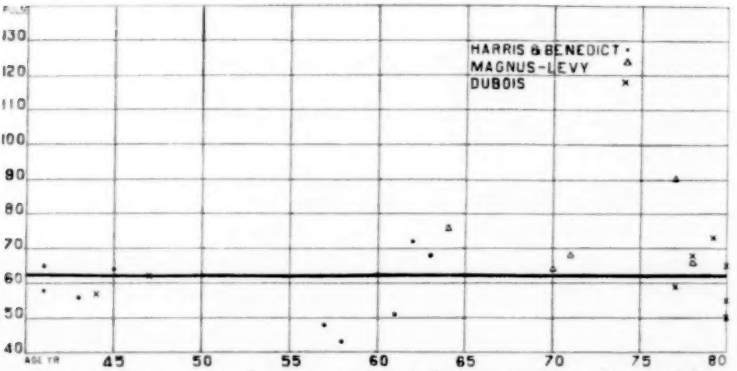

Chart 2.—Curve of basal pulse rate in relation to age for males, aged from 40 to 80 years. Source of the data is indicated by symbols.

drop during infancy with a more gradual decline during childhood and youth to the adult level of 62 at 20 years, at which point the pulse remains constant throughout the greater part of adult life with a possible slight tendency to rise in old age. It also shows the common range of variations and the greater, less common variations. Other points will be discussed in more detail later.

Charts 3 and 4 show the same thing for females. Again one notes the rapid drop in early childhood and the more gradual decline during later childhood. The adult level, reached at the age of 20 is 69, 7 beats higher than the average for adult men. The variations seem somewhat more marked than in the case of the men, and there is a paucity of observations after 35 years which makes the later averages of doubtful value.

COMMENT ON DATA

In order to study the starting point of the curve, we studied the pulse rate at birth and for the first 18 months of life. Most of the figures for this period are taken from Benedict and Talbot,[14] and we have nothing to add to what they have already said and shown. At birth they found the average pulse rate to be 112, a rate considerably lower than the 130 to 140 usually given as the average for the fetus. During the first week the rate rose approximately to that which we find at the end of the first year. During this year the rate varies in different persons and at different months, but there is no evidence of a definite trend, and the monthly variations seem to be without significance. In taking the averages for the year, we followed the rule which we had adopted for the other ages, using the rates for the months which were nearest to the first birthday. Thus we found the average to be 116 for boys and 122 for girls. The reason for this difference is not clear. Townsend,[39] in a series of 1,000 cases, found the average pulse rate at full term to be 140.26 for boys and 141.83 for girls. As there is no constant difference during the succeeding years, it seems a curious coincidence that the sex difference at one year should correspond so closely to the difference that we find in adult life.

At the other end of life the figures are very unsatisfactory, as few observations have been made on the pulse rate of the aged. We have no such series of cases as was reported by Pennock,[40] who studied 173 men between the ages of 50 and 90, and 203 women between the ages of 50 and 115. Our figures show a very slight increase in the pulse rate of old women and an almost negligible increase in that of the old men. As it is usually stated that the pulse rises slightly in old age, it may be worth while to give Pennock's figures, which, representing pulse rates under uniform but not basal conditions, are comparable only within his own series.

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39. Townsend, C. W.: Some Statistics on the Weight of Infants, Sex and Fetal Heart Rate, Boston M. & S. J. **134**:484-485, 1896.

40. Pennock, C. W.: Note on the Frequency of the Pulse and Respiration of the Aged, Am. J. M. Sc. **40** (o.s.) or **14** (n.s.) 68-75, 1847.

TABLE 3.—*Pulse Rate of Old Age (Pennock)*

Age	Men		Women	
	No. of Cases	Pulse	No. of Cases	Pulse
50– 60	59	70.04	36	73.55
60– 70	58	69.04	68	75.19
70– 80	35	70.04	55	78.28
80– 90	18	72.49	37	75.35
90–115	..	.....	7	76.56

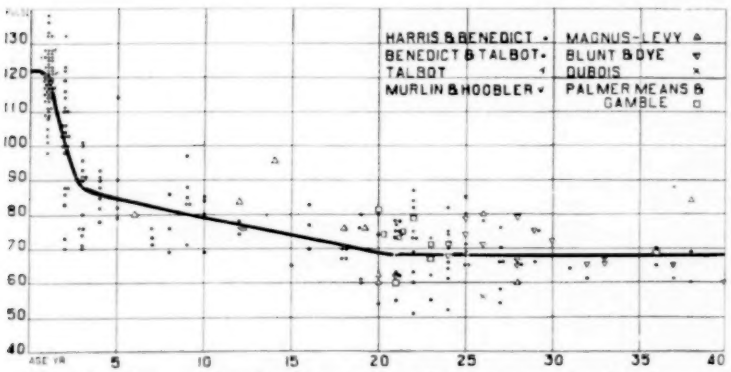

Chart 3.—Curve of basal pulse rate in relation to age for females, aged from 1 to 40 years. Source of data is indicated by symbols.

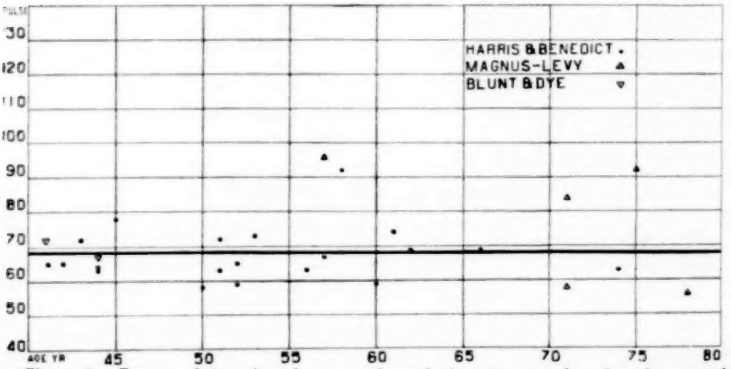

Chart 4.—Curve of basal pulse rate in relation to age for females, aged from 40 to 80 years. Source of data is indicated by symbols.

The differences certainly are not marked, and the question of determining which persons of this age have a normal circulatory system is difficult. Harris and Benedict [7] criticized DuBois' [36] old men as being abnormally healthy, and it is more than likely that no man over 60 is perfectly normal. Guy [3] realized this difficulty when he stated that the pulse rose in age, if feeble as well as robust men were studied.

The years between infancy and old age are those with which we are chiefly concerned, and it is during these years that the pulse rate is of special interest. We find the basal pulse rate to be 62 for adult men and 69 for adult women, figures which correspond closely with those given by Harris and Benedict,[7] by Addis,[18] by Korösy,[11] and by Blunt and Dye.[33] These figures are lower than those given by persons who studied the pulse under resting but not basal conditions, a finding which was predicted by Tigerstedt.[1] As the resting conditions given by different observers vary, it is obvious that different groups of observations are not comparable, and that in establishing a standard it is necessary to make the observations under standard conditions. As the conditions required for basal metabolism work are well known and widely used, they seem the logical conditions to adopt. In speaking of the basal pulse rate, basal must not be interpreted to mean minimal, for lower rates have been observed during sleep.[10] A detailed study of the sleeping pulse rate would be interesting, but difficult to carry out in a large series, and scarcely applicable to general use. The use of the basal pulse rate would make it evident that many careful studies undertaken to show the normal pulse rate give no indication of the resting normal, but instead show that, for one reason or another, the subjects were not in a state of rest. This applies not only to the older work, but to much recent work as that of Burlage,[41] who gives average pulse rates for a series of 1,700 girls and finds rates which are obviously high, possibly indicating that the examination caused a good deal of mental disturbance. Basal pulse standards would be of value as a starting point from which to determine the influence on the pulse rate of various factors.

The adult level is reached in both sexes at the age of 20, after a decrease in rate throughout childhood and adolescence. This decrease is more marked in the first two years and less marked later. Owing to the discussion (DuBois and Benedict) as to whether there is an increase in metabolism at or just before the time of puberty, the pulse rate at this time is interesting (Table 1). The figures of Volkmann,[2] which are not basal and which include observations made on boys and girls, show a continuous drop to the eleventh year, a very slight rise at the twelfth year with an almost constant rate for the next two years, followed by a progressive drop to 20 years. In this series the probability of variations is reduced by the fact that for any year there are from 54 to 107 observations. Katzenberger [42] shows no rise at puberty for either sex, either in his observations or in the figures which

41. Burlage, S. R.: Blood Pressure and Heart Rate in Girls During Adolescence, Am. J. Physiol. **64**:252-284 (April) 1923.

42. Katzenberger, A.: Puls und Blutdruck bei gesunden Kindern, Ztschr. f. Kinderh. **9**:167-195, 1913.

he collected from various sources. Our figures for boys show a rise at the thirteenth and fourteenth years, but the number of observations is small and most of them are those observations on the boy scouts [36] which Benedict [14] criticized as not made under basal conditions. A similar rise is observed in the case of Bailey's figures for clinic patients. We can show no rise for girls, but it is interesting to note that if we included Benedict and Hendry's [31] figures on the waking girl scouts, such a rise would be present, while if we used the figures obtained while the girls slept,[32] there would be a definite drop. In order to settle this question we believe that it is necessary to have a large number of notes made by one observer under strictly basal conditions.

For each period we must note, not only the average pulse rate, but the usual range of variations, realizing that this does not represent the limits of normal variation, but the ordinary differences which one is likely to find in any group of persons. As MacKenzie [5] says: "The pulse rate varies very considerably according to age, sex and individual peculiarities." Guy [3] gave the usual range of variation as 43 beats for men and 48 beats for women, but much greater variations are noted. This variation is shown in the charts and scarcely needs comment. In men, the usual pulse is between 50 and 70, a total range of 20 beats: rates under 50 and over 80 are decidedly uncommon. In women the usual pulse is between 60 and 80 beats to the minute; rates between 50 and 60 and between 80 and 90 occur occasionally; rates over 90 are rare; and no rate less than 50 was observed in this series. In a larger series it is probable that in a few cases a wider variation would be noted. For the first year the rates, for boys and girls alike are grouped between 108 and 128, but wide variations are noted, the range for boys being from 95 to 145, for girls from 84 to 165. During the second year the extreme variations for boys are from 84 to 127, for girls from 70 to 132. In the third year no rate over 110 was noted for either sex.

The difference between the pulse rate of men and of women is a matter of common knowledge and everyday observation. This difference does not depend on activity, but exists under basal conditions. In women the effect on the pulse rate of the menstrual cycle [43] has been considered and found to be inconstant or negligible, therefore it need not be considered in discussing these curves. The sex difference in pulse rate in childhood is very slight, and from the second to the tenth year we are able to show no constant and convincing difference.[44] After that, the rate is six or seven beats higher in the female, a difference which is rather less than we find given in most of the references

43. Zuntz, L.: Untersuchen über den Einfluss der Ovarien auf den Stoffwechsel, Arch. f. Gynäk. **78**:106-136, 1906.

44. Observations made by us since writing the foregoing indicate that there is a sex difference in the average basal pulse rate below the age of 10 years.

in the literature. Guy [3] gives a difference or from 6 to 14 beats at different periods, the average being 9. The important point, however, is not the numerical difference, simply the fact, long recognized, that the pulse of women is slightly more rapid and slightly more variable than that of men.

Through the kindness of Dr. Cameron V. Bailey of the Post-Graduate Hospital, we had access to his figures on a large series of basal metabolism determinations. Omitting all patients with a definite diagnosis, an abnormal metabolism, or any thyroid or cardiac disturbance, we obtained data on 301 supposedly normal males between the ages of 4 and 67, and 364 females between the ages of 4 and 68. We did not include these figures in our series because persons referred to a clinic are not those who would be selected as normal controls. We have used these figures for purposes of comparison, and find that the curve representing the average pulse rates for different years follows the same line as that for the normal controls but that it is always from 6 to 12 beats higher. The average for adult men is 73, 11 beats higher than that for the normal controls, while the average for women is 77 as compared with 68. There appears to be a slight rise at the time of puberty in the case of the boys, but no rise is noted in the case of the girls. The range of variations is slightly greater in the clinic patients than in normal subjects. The reason for these differences is not perfectly clear, but it may be that minor disturbances of the type which cause a patient some trouble but which remain undiagnosed by the doctor will cause a slight acceleration of the pulse rate. Possibly it is due to nervousness, the clinic patient expecting the doctor to find something wrong with him, while the normal control consents to the test to oblige the doctor.

The age curves of basal pulse rate and basal metabolic rate have been brought together in Chart 5 for purposes of comparison. The curve of metabolism of Aub and DuBois [8] is used. Since only the general outlines are discussed here, the statements are applicable as well to the standards of Harris and Benedict.[7] The rise indicated in the metabolism curve at puberty is not spoken of because it is the source of some difference of opinion on which the data can shed no light.

Superficially, the changes in pulse rate with age are similar to the changes in the metabolic rate with age. Both curves are high in infancy as compared with adult life. The resemblance would be even greater if the age-curve of metabolism prepared by Benedict [45] were used, since the highest point is more narrow and is placed at an earlier age, between

45. Benedict, F. G.: Energy Requirements of Children from Birth to Puberty, Boston M. & S. J. **181**:107-139 (July 31) 1919.

1 and 2 years. In the two sexes there is a difference of 10 per cent. in basal pulse rate (about 7.1 beats per minute) and of 7 per cent. in basal metabolic rate.

On short examination, however, a number of differences are seen. The pulse is high in infancy while the metabolism is as low as that of adults. This discrepancy is even more marked in the premature infants studied by Talbot, Sisson and Moriarty,[17] in which the metabolism was exceptionally low while the pulse rate was even higher than that of the fetus. In adults the pulse rate remains the same, while metabolic rate drops at a slow but constant rate through life. In regard to sex differences, while the amount of difference in pulse rate and metabolism is

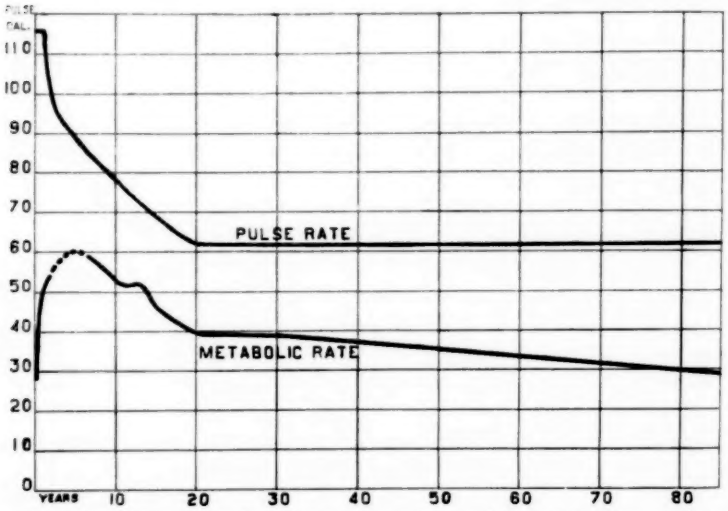

Chart 5.—Curve of basal pulse rate for males, aged from 1 to 80 years, from Charts 1 and 2, above, compared to the curve of basal metabolism per square meter of body surface hourly for males, from Aub and DuBois.

numerically similar, males with lower pulse rate have higher metabolism and women with higher pulse rate have lower metabolism. This is contrary to the changes in subjects in whom the higher pulse rate is associated with metabolism also high.

This discussion is based on 736 observations made under the strict basal conditions used in experimental work by well known observers. The curve for males includes 361 observations, the curve for females, 375. As has already been mentioned, not all age groups are equally well represented. In making the average for adult males, 146 observations were used; for adult females, 85 observations were used. The average rate at one year was based on 62 and 58 observations, respectively, for males and females.

We believe that a knowledge of the basal pulse rate and the normal variations at all ages is of importance to the increasing number who make and interpret basal metabolism determinations. Evidence is accumulating that the pulse rate is a rough guide to the metabolism. A number of the persons visited by a physician were resting in bed, and had taken no food for a number of hours. Under these circumstances, a comparison of the pulse rate to the average found under basal conditions is more accurate than comparison to the old values determined under conditions of partial rest.

CONCLUSIONS

1. The average basal pulse rate, in adults aged from 20 to 40 years, is 62 for males and 69 for females.

2. The average basal pulse rate at 1 year is 116 for males and 122 for females.

3. The curve of average basal pulse rate drops rapidly for the first three years of life, then less rapidly to the adult level reached at 20 years of age.

4. The variability of the pulse rate under basal conditions is greater in children than in adults, and greater in females than in males.

5. The average basal pulse rate of females is greater than that of males at all age periods after 10 years in the data assembled here. It varies from 4 to 11, with an average of 7 beats a minute.

THE SUGAR CONTENT OF THE CEREBROSPINAL FLUID AND ITS RELATION TO THE BLOOD SUGAR *

GEORGE M. GOODWIN, M.D.
AND
HAROLD J. SHELLEY, M.D.
NEW YORK

During the last four years, the prevalence of encephalitis with its attendant diagnostic difficulties has brought out the importance of the quantitative determination of sugar in the spinal fluid. Kraus and Pardee [1] state that they found this the one finding of any positive value in a large percentage of spinal fluids from encephalitic patients. Because of the stress laid on this point in the literature, we started making routine sugar determinations on the spinal fluids in all cases in which the possibility of encephalitis was considered (Table 2), but we soon found that we had no way of knowing whether the figure obtained for the sugar content of the spinal fluid was normal. The literature gave us no help because of the great variation in the figures given for the normal sugar content in spinal fluid.

We therefore undertook a study of the sugar content of the cerebrospinal fluid with particular attention to the following points:

1. Does the sugar content of the cerebrospinal fluid remain constant in the same individual?

2. Is there a level which, within reasonable limits, might be considered normal for different individuals?

3. Is there any relation between the sugar content of the cerebrospinal fluid and that of the blood and, if so, is this relationship constant?

4. What influence has the ingestion of carbohydrates on the sugar content of the cerebrospinal fluid, and on the relation between the sugar content of the cerebrospinal fluid and the blood?

5. If there is a definite relation between the sugar content of the cerebrospinal fluid and the blood, what variations from this relation are found in pathologic conditions of the central nervous system, and can these changes be attributed to any definite causes?

In our work, the figures are given in milligrams per hundred cubic centimeters of cerebrospinal fluid or blood, as determined by the Benedict colorimetric method.

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* From St. Luke's Hospital.

1. Kraus, W. M., and Pardee, I. H.: Arch. Neurol. & Psychiat. **5**:710 (June) 1921; Acute Epidemic Encephalitis, Tr. A. Research in Nervous and Mental Diseases, 1921, p. 99.

1. INDIVIDUAL VARIATIONS IN THE SUGAR CONTENT OF THE CEREBROSPINAL FLUID

Our results would indicate that the sugar content of the cerebrospinal fluid is not constant in the same individual. As shown by the tables, estimations made on successive mornings after a night's fasting showed variations of from 4 to 16 mg.

2. SUGAR CONTENT LEVEL OF THE CEREBROSPINAL FLUID IN DIFFERENT INDIVIDUALS

Most investigators have assumed that there is a level of sugar content of the cerebrospinal fluid which, within reasonable limits, might be considered normal. That there is some error in this assumption is indicated by the great variation in the conclusions of different investigators as to the normal figure, and also by the wide variation of the normal figures given by each of several persons. Nawratzki [2] (1897) considered 46 mg. per hundred cubic centimeters of spinal fluid as normal. In 1909, von Jaksch reported twenty cases with the sugar content of the cerebrospinal fluids ranging between 60 and 80 mg. per hundred cubic centimeters of spinal fluid. In 1912, Mestrezat [3] concluded that the normal level varied between 48 and 53, and, in 1920, Marie and Mestrezat [4] showed that their idea was unchanged. In 1913, Kopetsky [5] reported eight cases with an average of 46. In 1915, Hopkins,[6] using the modified Bang's micromethod, concluded that the normal level was between 60 and 75. In 1921, Coope [7] reported the sugar content of the cerebrospinal fluid of three normal people at 64, 69 and 83. He did not state the time of taking the fluid. In 1921, Foster,[8] using the Folin-Wu method, reported the variation in twenty-two normal spinal fluids as lying between 44.2 and 61.4, with an average of 52.8. In 1923, Kelley [9] concluded from a study of the sugar content of the spinal fluids in 1,000 cases that the sugar content of normal spinal fluid lies between 40 and 95 mg. per hundred cubic centimeters of cerebrospinal fluid. He makes no statements as to the time at which the spinal fluids were taken, or as to the relation to the blood sugar.

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2. Nawratzki: Zur Kenntniss der Cerebrospinal flussigkeit, Ztschr. f. physiol. Chem., 1897, p. 533.

3. Mestrezat: J. de physiol. et de path. gen., Paris, **14**:504, 1912.

4. Marie, P., and Mestrezat: Bull. de l'Acad. de méd., Paris, **83**:103 (Feb. 3) 1920.

5. Kopetsky: Ztschr. f. Ohrenh. **68**:1-19, 1913.

6. Hopkins: Am. J. M. Sc. **150**:847 (Dec.) 1915.

7. Coope, R.: Quart. J. Med. **15**:1 (Oct.) 1921.

8. Foster, H. E.: Hyperglycorachia in Encephalitis, J. A. M. A. **76**:1300 (May 7) 1921.

9. Kelley, A. G.: Serology of Spinal Fluid and Blood in Encephalitis, Southern M. J. **16**:407 (June 23) 1923.

Our figures indicate that there is no normal level for the sugar content of the cerebrospinal fluid, except within very wide limits. In the ordinary cases, the figures varied from 40 to 77 mg. per hundred cubic centimeters of cerebrospinal fluid. In disturbances of the central nervous system (Table 4), the sugar content varied from 47 to 105 mg. per hundred cubic centimeters. Cases of cerebrospinal syphilis (Table 5) showed variations of from 38 to 74 mg. per hundred cubic centimeters. In the diabetic cases with no pathologic condition of the central nervous system, the figures ranged from 80 to 200 mg. per hundred cubic centimeters (Table 7).

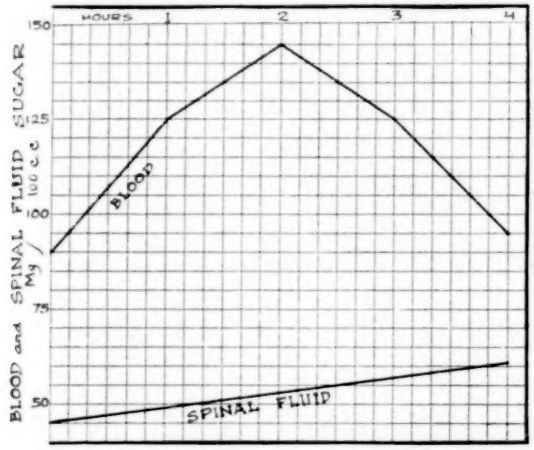

Chart 1.—Blood and spinal fluid sugars before and after breakfast.

3. RELATION BETWEEN THE SUGAR CONTENT OF THE CEREBROSPINAL FLUID AND THE SUGAR CONTENT OF THE BLOOD

Notwithstanding this wide variation in the sugar content of the cerebrospinal fluid, the charts appear to show a definite relation between the cerebrospinal sugar and the blood sugar. But few investigators have suggested a definite relationship between the blood sugar and the cerebrospinal fluid sugar. Hopkins [6] appears to have been one of the first, if not the first, to notice that there was some relation between the sugar content of the cerebrospinal fluid and of the blood. Using the modified Bang's micromethod, he concluded that the normal spinal fluid sugar level was between 60 and 75. Although his figures varied so greatly that his idea was far from proved, he concluded that the normal spinal fluid sugar was approximately 10 mg. less than the blood sugar. Neuberg stated that the spinal fluid sugar was the same as that of the blood. In 1916, Weston, using the method of Myers and Bailey, found

in a series of experiments that the cerebrospinal fluid sugars varied from 60 to 70, with the blood sugars in the same cases varying between 100 and 120. The relative times of taking the cerebrospinal fluid and the blood were not stated, however.

The more recent figures in the literature disagree entirely with the conclusions of Hopkins and Neuberg. From the figures given by Thalheimer and Updegraff [10] (1922) in reporting the spinal fluid sugars and the blood sugars of six normal cases, we find the results given in Table 1. Both spinal fluid and blood were taken before break-

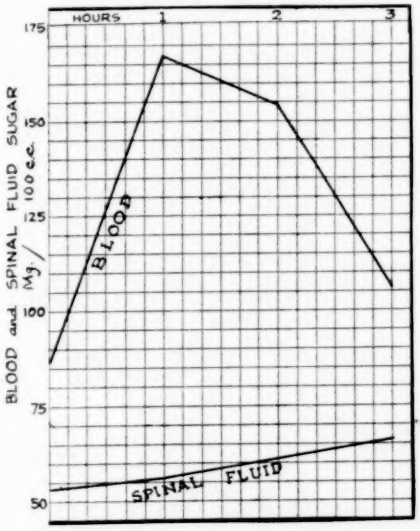

Chart 2.—Blood and spinal fluid sugars before and after glucose tolerance tests.

fast, after a night's fasting. These cases show a fairly constant percental relation between the sugar content of the spinal fluid and of the blood, the average figure being 46 per cent. This finding agrees with the conclusion of Wilcox and Lyttle [11] (1923) that the normal cerebrospinal fluid sugar is, with some variation, half that of the blood sugar.

Palonavski and Duhot [12] (1923) showed a definite relation between the sugar content of the cerebrospinal fluid and of the blood. By their method of determination of blood sugars, the blood sugars, in a series

10. Thalheimer, W., and Updegraff, H.: Comparison of Several Clinical Quantitative Blood Sugar Methods, Arch. Neurol. & Psychiat. **8**:15 (July) 1922.
11. Wilcox, H. B., and Lyttle, J. D.: Arch. Pediat. **40**:215 (April 23) 1923.
12. Palonavski, M., and Duhot, E.: Presse méd. **31**:60 (Jan. 20) 1923.

TABLE 1.—*Spinal Fluid Sugars and Blood Sugars in Six Normal Cases (Thalheimer and Updegraff)*

Case	Blood Sugar	Spinal Fluid Sugar	Percental Relation Spinal Fluid Sugar to Blood Sugar
1	135	55	40.7
2	158	74	46.4
3	129	63	48.8
4	...	64	....
5	115	53	46.0
6	117	56	47.8

TABLE 2.—*Spinal Fluid Sugars*

				Spinal Fluid						
				Cells				Wassermann		
No.	Age	Diagnosis	Date	Total	P.*	L.*	Globulin		Sugar	Remarks
1	59	Encephalitis	3/30/23	..	..	2	+	0	71	Necropsy; many cerebral hemorrhages
			4/ 7/23	..	..	2	0	0	74	
			4/11/23	11	4	7	0	0	58	
			4/19/23	22	3	19	+	0	53	
2	11	Encephalitis	.....	..	..	4	0	0	74	
3	26	Encephalitis	2/14/23	30	4	26	+	0	53	
			2/21/23	27	2	25	+	0	53	
4	30	Encephalitis	1/ 4/23	43	2	41	0	0	67	
			1/ 5/23	18	2	17	0	0	61	
			3/11/23	..	..	7	++	0	60	
			3/12/23	..	..	4	0	0	63	
5	30	Encephalitis (striate and psychic type)	1/23/23	..	..	15	0	0	80	
			1/27/23	..	..	14	0	0	95	
6	31	Postencephalitic asthenia	.....	..	..	5	+	0	50	
7	13 mos.	Tuberculous meningitis	9/14/23	60	10	90	++++	0	Too small to estimate	
8	36	Tuberculous meningitis ?	8/28/23	195	127	68	++	0	57	Positive in guinea-pig; December 1, patient alive, up and about
			8/30/23	111	11	100	+++	0	46	
			9/ 2/23	195	..	..	+	0	57	
9	60	Pachymeningitis internal hemorrhagica	3/15/23	..	1	4	0	0	71	Necropsy
				9	2	4	0	0	80	(Red blood cells 3)
10	10	Poliomyelitis; facial paralysis	8/17/23	13	2	11	++	0	40	
			8/20/23	16	4	12	++	0	24	After serum
				7	1	6	++	0	48	
11	39	Carcinoma of bronchus with edema of brain	10/10/23	..	..	5	+	0	70	Spinal fluid bloody
			10/17/23	530	..	..	+++	0	20	After serum (necropsy)
12	13 mos.	Acute ileocolitis (encephalitis?)	9/16/23	..	..	5	0	0	50	
			9/23/23	..	..	1	0	0	58	
13	9	Infected left antrum	.....	..	..	47	0	0	44	
14	16	Epilepsy	.....	..	..	4	+	0	62	
15	50	Chronic tonsillar and oral sepsis	.....	..	..	4	0	0	40	
16	40	Malta fever	.....	5	1	4	0	0	43	
17	41	Syringomyelia	.....	13	6	7	0	0	50	Blood in spinal fluid
18	23	Malignant endocarditis (staphylococcus), with hemiplegia	2/ 8/23	268	236	32	+	0	63	Necropsy
19	53	Cerebrospinal syphilis with optic atrophy (treated)	1/15/23	400	302	88	+++	0	42	Spinal fluid contained hemolyzed blood. On 10/12/24 blood Wassermann reaction was ++++ and spinal fluid Wassermann 0

* In this and the following tables, P., under cells, indicates polymorphonuclears, and L., lymphocytes.

of ordinary cases, ranged from 52 to 88, which was uniformly slightly higher than the spinal fluid sugars which ranged from 45 to 85. The administration of epinephrin to patients giving a hyperglycemia produced a rise in the spinal fluid sugar, which did not return to normal until after the blood sugar had returned to normal. They concluded that the relation between the spinal fluid sugar and the blood sugar was important, but that the spinal fluid sugar figure alone was not of value.

Our figures in Table 9 would indicate that the findings of Thalheimer and Updegraff,[10] which are borne out by Wilcox and Lyttle,[11] are essentially correct. The percental relation of spinal fluid sugar to blood sugar in the sixteen determinations in the ordinary cases falls

TABLE 3.—*Spinal Fluid and Blood Sugars in Ordinary Cases*

No.	Age	Diagnosis	Spinal Fluid				Blood Sugar	Percental Relation Spinal Fluid Sugar to Blood Sugar	Remarks
			Cells L.	Globulin	Wassermann	Sugar			
1	65	Arteriosclerosis	1	0	0	49	105	47	
2	51	Bronchial asthma; chronic cardiovascular disease	1	0	0	43	88	49	
3	70	Chronic cardiovascular disease	2	±	0	62	118	52	
4	30	Cardiac hypertrophy and decompensation	2	+	0	55 45	100 90	55 50	
5	25	Chronic cardiovascular disease	6	0	0	57	100	57	
6	64	Cancer of the stomach	4	+	0	52	105	50	
7	65	Cancer of sigmoid	3	0	0	55	105	52	
8	49	Colitis	6	+	0	40	86	46	
9	48	Duodenal ulcer	1	+	0	77	118	65	
10	56	Hypertension; chronic nephritis	1	+	0	67	105	63	
11	55	Hyperacidity	1	+	0	48	84	57	
12	22	Chronic polyarthritis	...	..	...	50	100	50	
13	36	Tuberculosis of lungs and spine; tertiary syphilis	1	0	0	48	95	50	Blood Wassermann ++++
14	52	Duodenal ulcer	5	+	Anticomplementary, probably negative	54	95	57	
15	16	Lobar pneumonia	1	0	0	51	110	46	

within the limits of 45 and 65 per cent., giving an average figure of 53 per cent. Of the eight determinations in the treated cerebrospinal syphilis cases, all but one lie between 45 and 65 per cent., giving an average of 55 per cent. The six determinations in the diabetic cases also fall between 45 and 65 per cent., with an average figure of 55 per cent. Of the twelve determinations in ordinary diseases of the central nervous system (Table 4), only one lies below 45 and two above 65 per cent., giving an average figure of 57.7 per cent. We find, therefore, that, in a total of forty-two determinations, only one lies below and three above the limits of 45 and 65 per cent., the average being 54.8 per cent. This constant percental relation is found notwithstanding the great variation in the sugar content of the cerebrospinal fluid and of the blood, as expressed in milligrams per hundred cubic centimeters.

These figures would indicate that there is a definite relationship between the cerebrospinal fluid sugar and the blood sugar, and that the figure representing this relationship, stated as the percental relationship between the two, is relatively constant, lying between 45 and 65 per cent. This may be considered a reasonable variation, provided determinations are made on both blood and cerebrospinal fluid taken at the same time, after a night's fasting.

4. INFLUENCE OF THE INGESTION OF CARBOHYDRATES ON THE SUGAR OF THE CEREBROSPINAL FLUID AND ITS RELATION TO THE BLOOD SUGAR

In 1920, Isamu Ino [13] worked out carefully in rabbits the effect of the carbohydrate intake on the sugar content of the cerebrospinal fluid

TABLE 4.—*Pathologic Conditions of the Central Nervous System Without Change of Relation of Cerebrospinal and Blood Sugar Content*

No.	Age	Diagnosis	Spinal Fluid				Blood Sugar	Percental Relation Spinal Fluid Sugar to Blood Sugar	Remarks
			Cells	Globulin	Wassermann	Sugar			
1	53	Cancer of stomach with hemorrhage into floor of 4th ventricle	1 L	0	0	47	100	47	Necropsy
2	70	Hemiplegia; cerebral thrombosis	2 L	+	0	52	100	52	
3	43	Hemiplegia.....	30	+	0	57	100	57	Fluid contained hemolyzed blood
			P 13, L 17 6	+	0	53	87	61	Fluid yellow
4	19	Manic depressive psychosis	P 2, L 4 4 L	0	0	50	80	62	
5	40	Unexplained headaches; chronic malaria	1 L	0	0	57	83	69	
6	28	Alcoholic neuritis	5 L	++	0	57	83	69	
7	64	Urticaria; uremia	2 L	0	0	74	118	62	(In delirium)
						64	118	53	(Normal)
8	72	Uremia; auric fibrillation	5 L	0	0	83	188	44	No glycosuria
9	59	Uremia; auric fibrillation	6 P 5, L 1	+	0	67	105	63	Spinal fluid bloody
10	..	Uremia; chronic glomerular nephritis; hypertension	1 L	0	0	105	200	52	No glycosuria

and the relation between the changes resulting and the changes in the blood sugar. In his work, the blood sugar reached its highest point immediately after the intravenous injection of the carbohydrate—1 gm. of glucose, galactose or lactose per kilogram of body weight—returning to normal within an hour. The spinal fluid sugar did not reach its maximum until one hour after the injection, and then required four hours to return to normal.

Due to the impracticability of doing any great number of lumbar punctures on any one patient, we were unable to obtain any curves of

13. Ino, Isamu: Acta Scholae Medicinalis, Univ. Kioto, No. 4, March 25, 1920-1923, p. 609.

great length, but the changes we observed in our work did not take place as rapidly and were not as great as those obtained by Ino in his work on rabbits. This is probably explained by the fact that, in his work with rabbits, Ino took the cerebrospinal fluid from the base of the skull. Any changes due to fluid of a different composition coming from the choroid plexus should register more quickly there than in the fluid obtained from the lumbar region in man, both because of the lesser distance of flow and the smaller quantity of the original spinal fluid by which it would be diluted.

In our work, blood and cerebrospinal fluid were taken at the same time after the patient had fasted over night. An ordinary hospital

TABLE 5.—*Pathologic Conditions of the Central Nervous System in Which Changes Have Been Reported in the Cerebrospinal Fluid Sugar*

				Spinal Fluid					Percental Relation Spinal Fluid Sugar to Blood Sugar	
No.	Age	Diagnosis	Date	Cells	Globulin	Wassermann	Sugar	Blood Sugar		Remarks
1	29	Encephalitis	11/18/23	8 L	++	0	54	96	56	
			11/28/23	11 P 5, L 6	++	0	70	105	66	
			12/10/23	11 L	++	0	56	105	53	
			12/19/23	....	..	...	54	105	53	
2	70	Herpes zoster; diabetes mellitus	11/17/23	2 L	0	0	55	176	31	Two days before rash
			12/17/23	3 L	0	0	95	185	51	Three weeks after rash
3	65	Acute purulent leptomeningitis from sinuses	.....	2 L	0	0	63	100	63	Spinal fluid sugar 3 hours after breakfast; blood sugar fasting; necropsy
4	37	Pulmonary tuberculosis; tuberculous meningitis	12/ 7/23	84 L 79, P 6	+++	0	Too small to estimate	134	..	Blood Wassermann reaction, cholesterinized antigen 4+, acetone insoluble antigen 0
			12/ 8/23	90 L 73, P 17	+++	0	15	143	10	Repeated blood Wassermann reaction, cholesterinized antigen 4+, acetone insoluble antigen 0; necropsy
5	52	Diabetes; thrombosis of lateral sinus with pneumococcus Type III, blood culture	.....	1 L	0	0	134	236	56	Before
				2 L	0	0	84	200	42	At height of symptoms

breakfast or the routine glucose test of 1.5 gm. of glucose per kilogram of body weight was given the patient, and the blood and spinal fluids taken simultaneously before and at different periods afterward, as indicated in Table 8.

In every case, there was a small but definite rise in the cerebrospinal fluid sugar content. This varied from 7 to 16 mg. in the five cases. The rise in blood sugar was temporary only, so that cerebrospinal fluid with an increased sugar content would be "secreted" only during that period. This would then be diluted by the fluid already present, and the rise as noted in the fluid from the lumbar region would not only be decreased by this dilution, but also would appear later than the rise in the blood

sugar content, as the fluid with the higher sugar content must flow or diffuse down to the lumbar region.

In our five cases, the rise is small as compared to the rise in the blood sugar, but it is constant and definite. As in the case of Ino's rabbits, the maximum rise occurs some time after the maximum rise in the blood sugar. In the one case which we ran for six hours, the maximum rise was reached at the end of four hours with the return to normal at the end of six hours.

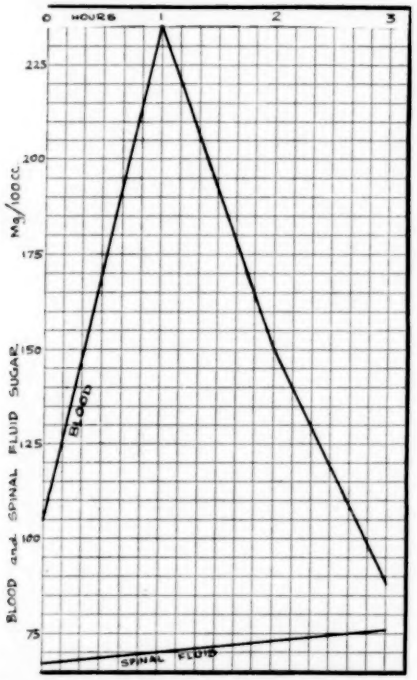

Chart 3.—Blood and spinal fluid sugars before and after glucose tolerance tests.

The extent to which the relation of cerebrospinal fluid sugar to blood sugar is disturbed by the ingestion of carbohydrate is shown by the figures in Table 8. The percentages, instead of lying between 45 and 65, range from 33 to 82. That this is due both to an early rise in the blood sugar and a late rise in cerebrospinal fluid sugar is shown by the fact that the range is both lower and higher than the fasting relationship. The fact that the percental relationship between the cerebrospinal fluid sugar and the blood sugar is thrown off by food intake

demonstrates the necessity of making these determinations at the same time after a night's fasting. Determinations made at other times are of no value.

5. VARIATION OF PERCENTAL RELATIONSHIP IN PATHOLOGIC CONDITIONS OF THE CENTRAL NERVOUS SYSTEM

The literature contains many reports of the sugar content of the cerebrospinal fluid in pathologic cases. With a few exceptions, these appear to have but little value, and in most of these cases no attempt is made to show whether or not the blood sugar was normal. In only one instance were uniform conditions used in taking the blood and spinal fluid.

TABLE 6.—*Spinal Fluid and Blood Sugars in Cerebrospinal Syphilis*

			Spinal Fluid					Percental Relation Spinal Fluid Sugar to Blood Sugar	
No.	Age	Diagnosis	Cells L.	Globulin	Wassermann	Sugar	Blood Sugar		Remarks
1	38	Cerebrospinal syphilis, untreated; gastric crisis	80	++	C.* ++++ A.-I. +++	38	110	33	Blood Wassermann reaction ++++
2	56	Cerebrospinal syphilis; tabes treated	3	÷	0	48	95	50	
3	47	Cerebrospinal syphilis; tabes treated	3	+	C. +++ A.-I. 0	58	108	53	Blood Wassermann reaction 0; in 1918 ++++
						51	105	51	
4	66	Cerebrospinal syphilis; tabes treated	10	++	Anticomplimentary	55	90	61	Blood Wassermann reaction ++++
5	72	Cerebrospinal syphilis; tabes treated	6	0	0	74	100	74	
6	60	Tertiary syphilis; transitory aphasia and hemiplegia, treated	1	0	0	54	100	54	Blood Wassermann reaction 0; in 1914 was 4+
7	..	Congenital syphilis, treated 6 years	3	0	0	48	95	50	Blood Wassermann reaction 0; in 1917 was 4+
8	..	General paralysis, treated	1	++	0	53	105	50	

* C. indicates cholesterinized antigen; A.-I., acetone insoluble antigen.

It has been definitely shown that, in meningitis due to tuberculosis, staphylococcus or meningococcus, there is nearly always an actual fall in the cerebrospinal fluid sugar. In 1895, Quincke [14] reported that the reducing substances in the spinal fluid may disappear in meningitis. Articles by Coope,[7] Thalheimer and Updegraff,[10] and Wilcox and Lyttle [11] contain typical figures for meningococcus, staphylococcus and tuberculous meningitis cases. In the two latter articles, the authors showed that this decrease was unaccompanied by a decrease in the blood sugar, demonstrating that there is an actual fall in the percental relation of the sugar content of the blood and of the cerebrospinal fluid. The

14. Quincke: Ueber Lumbal punktion, Berl. klin. Wchnschr., 1895, No. 41.

fall in the sugar content of the cerebrospinal fluid and the fall in the percental relation of the sugar contents of the blood and of the cerebrospinal fluid are noted in Case 7 of Table 2 and in Case 4 of Table 5. Case 8 of Table 2 was probably a mistake in diagnosis as the subsequent course of the case would make the diagnosis of anterior poliomyelitis much more probable, although injection into a guinea-pig resulted in positive tuberculous lesions. The spinal fluid sugar findings bear this out.

It is interesting to note that the cerebrospinal fluid sugar was lowered by the injection of antimeningococcus serum (Table 2). This was probably due to dilution, although Ino,[13] in a series of experiments on human cerebrospinal fluid, in test tubes and in rabbits, showed that the reduction of spinal fluid sugar was proportionate to the number of white blood cells per cubic millimeter, and that all bacteria excited more

TABLE 7.—*Spinal Fluid and Blood Sugars in Diabetic Patients*

			Spinal Fluid					Percental Relation Spinal Fluid Sugar to Blood Sugar	
No.	Age	Diagnosis	Cells L.	Globulin	Wassermann	Sugar	Blood Sugar		Remarks
1	66	Diabetes; chronic nephritis	2	0	0	Lost 108	238 182	.. 56	
2	51	Diabetes; cholecystitis; pancreatitis	1	0	0	200	315	60	
3	45	Diabetes; tertiary syphilis	1	0	0	93	170	54	Blood Wassermann reaction ++++
4	52	Diabetes.....	1	0	0	134	238	56	
5	51	Diabetes mellitus	2	0	0	80	154	52	
6	70	Diabetes mellitus	2	0	0	95	185	51	

or less decomposition of the sugar in vitro, but not in proportion to the number of bacteria per cubic centimeter. He also showed that, in rabbits, the spinal fluid sugar was not reduced by starvation unless the rabbits were in a weakened condition.

In work with other cases, these investigators found no important lowering of the cerebrospinal fluid sugar, except in one type of cases. In 1923, Kelley [9] reported an average sugar content of the spinal fluid of 21 mg. per hundred cubic centimeters in 195 untreated cases of syphilis of the central nervous system; after treatment, in 100 cases, the average was 62. Our one case of untreated cerebrospinal syphilis gives a low figure and low percentage, agreeing with the figures of Kelley. The treated cases fall within normal limits.

Epidemic encephalitis is the disease in which the greatest amount of work has been done on the changes in cerebrospinal fluid sugar. In 1920, Dopter [15] reported a case with a cerebrospinal fluid sugar of 85,

15. Dopter, C.: Bull. de l'Acad. de méd. **83**:203 (March 2) 1920.

from which he concluded that the high sugar content was of diagnostic importance in differentiating the disease from acute or tuberculous meningitis, but that it was not pathognomonic nor even a constant finding in encephalitis lethargica.

In 1920, Netter [16] reported six cases with cerebrospinal fluid sugar figures varying from 70 to 97, with an average of 86. In 1920, Laporte and Rouzaud [17] reported twelve cases in which the cerebrospinal fluid

TABLE 8.—*Blood and Spinal Fluid Sugar Content After Ingestion of Glucose or Food*

			Spinal Fluid					
No.	Age	Diagnosis	Cells	Globulin	Wassermann	Sugar	Blood Sugar	Percental Relation Spinal Fluid Sugar to Blood Sugar	Remarks
1	30	Cardiac hypertrophy and decompensation	2 L	+	0	45	90	50	Fasting
						..	125	..	One hour after breakfast
						..	140	..	Two hours
						..	125	..	Three hours
						..	95	64	Four hours
2	43	Hemiplegia	50	+	0				
			P 13, L 17	(Fluid contained hemolyzed blood)					
			6	±	0	52	87	61	Fasting
			P 2, L 4	(Fluid yellow)					
						56	167	33	One hour after glucose test
						..	154	..	Two hours
						66	111	60	Three hours
3	53	Hypertension; chronic nephritis	1 L	+	0	67	105	64	Fasting
						..	235	..	One hour after glucose
						..	150	..	Two hours
						76	87	85	Three hours
4	19	Manic depressive psychosis	4 L	0	0	50	80	62	Fasting
						56	150	37	One hour after glucose
						59	72	82	Two hours
						..	83	..	Three hours
5	47	Cerebrospinal syphilis (treated 7 years)	3 L	+	±	51	105	48	Fasting
						..	190	..	One hour after glucose
						51	105	48	Two hours
						57	90	63	Four hours
						50	100	50	Six hours

sugar varied from 66 to 101, giving an average of 88. Coope [7] found ninety-two cases reported in the literature of 1920, in which only seventeen, or 18 per cent., showed figures of 55, or less. The variations were as follows: Seven cases showing from 100 to 110 mg. of sugar per hundred cubic centimeters of spinal fluid; thirteen cases showing from 90 to 99 mg.; twenty-five cases showing from 80 to 89; twenty, from 70 to 79; eight, from 60 to 69; twelve, from 50 to 59; six, from 40 to 49, and one from 30 to 39.

In 1921, Foster [8] reported eleven cases of encephalitis lethargica, in six of which blood sugar estimations were made. The relative time of

16. Netter, A.: Bull. et mém. Soc. méd. d. hôp. de Paris **44**:441 (March 26) 1920.

17. Laporte and Rouzaud: Bull. et mém. Soc. méd. d. hôp. de Paris **44**:422 (March 19) 1920.

taking the blood and the cerebrospinal fluid was not stated. Using the Folin-Wu method, the cerebrospinal fluid sugars varied from 53.5 to 113, and the blood sugars from 70 to 100. Of these spinal fluid sugars, only one came within the limits found in the sugar content of twenty-two normal spinal fluids, although the blood sugars lay within the normal limits.

In 1921, Kraus and Pardee [1] reported twelve cases of encephalitis lethargica with cerebrospinal fluid sugars varying from 62 to 95. Of these cases, all but two had blood sugars below 120; in these two cases, the blood sugars were 143 and 190. These investigators thought that

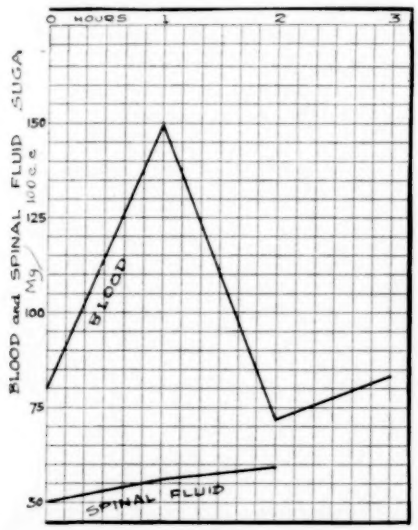

Chart 4.—Blood and spinal fluid sugars before and after glucose tolerance tests.

encephalitis caused vascular lesions which made the walls more permeable to sugar. In the same year, Coope [7] reported eleven cases of encephalitis lethargica, with spinal fluid sugars varying from 54 to 94, the average being 74.

Hirsch [18] (1921) thought that the high spinal fluid sugar might be due to hyperglycemia, since the intravenous injection of bacteria in animal experimentation gave a hyperglycemia. He also stated that acute infectious diseases caused a hyperglycemia. This would be indicated by the cases reported by Thalheimer and Updegraff [10] (Table 10), as the percental relation between the spinal fluid sugar and the blood sugar is

18. Hirsch, E. F.: J. Infect. Dis. **29**:40 (July) 1921.

TABLE 9.—*Percental Relation of Spinal Fluid Sugar to Blood Sugar in All Cases Studied*

Case	Number of Determinations Made	Average Relation, per Cent.	Number of Cases with Relation			
			44 per Cent.	45-55 per Cent.	56-65 per Cent.	66 per Cent.
Ordinary	16	54	0	11	5	0
Pathologic conditions of central nervous system without change in relation	12	57.7	1	4	5	2
Treated central nervous system syphilis	8	55	0	6	1	1
Diabetes	6	55	0	3	3	0
Total	42	54.8	1	24	14	3

TABLE 10.—*Results Obtained by Thalheimer and Updegraff in Work on Encephalitis Cases* *

Number	Time Taken	Blood Sugar	Spinal Fluid Sugar	Percental Relation Spinal Fluid Sugar to Blood Sugar
1	After breakfast	...	161	..
	Before breakfast	297	177	57
2	After breakfast	182	126	69
	Before breakfast	196	134	68
	Before breakfast	208	117	56
	Before breakfast	150	71	47
3	Before breakfast	174	89	51
	Before breakfast	144	82	57
4	Two hours postmortem	...	79	..
5	Four hours after breakfast	188	90	48
6	Before breakfast	159	80	50
7	Before breakfast	155	93	60
		163	84	51
8	Ten hours antemortem	226	125	55
9	Three hours after lunch	211	80	33
10	Before breakfast	148	84	57
11	Before breakfast	173	..	..
	Before breakfast	179	85.4	47
	Before breakfast	130	..	..
12	Before breakfast	115	56	48
13	Four hours after lunch	...	82	..
14	Five hours antemortem	...	136	..

* Since, according to our findings, the relation between the cerebrospinal fluid sugar and the blood sugar is thrown off by the ingestion of food, only those determinations made on the fluid and blood taken before breakfast are of value. The figures stating percental relation were added by us.

TABLE 11.—*Results Obtained by Wilcox and Lyttle in Work on Encephalitis Cases*

Number	Age	Blood Sugar	Spinal Fluid Sugar	Percental Relation Spinal Fluid Sugar to Blood Sugar
1	7	...	111	..
		98	57	61
		111	51	46
2	7	102	98	96
		...	87	85 ?
		...	79	77 ?
3	11	143	121	71
		101	66	65
4	11	125	89	71
		95	71	74

practically undisturbed. In contrast to this, Wilcox and Lyttle [11] found the cerebrospinal fluid sugar high in relation to the blood sugar in practically all their cases, although the relative time of taking the spinal fluid and the blood was not stated (Table 11).

In the one case of encephalitis which we have had since we began to work out the relation of the cerebrospinal fluid sugar to the blood sugar, the percental relation fell within the expected limits. Some of the other cases (Table 2) gave high figures for the sugar content of

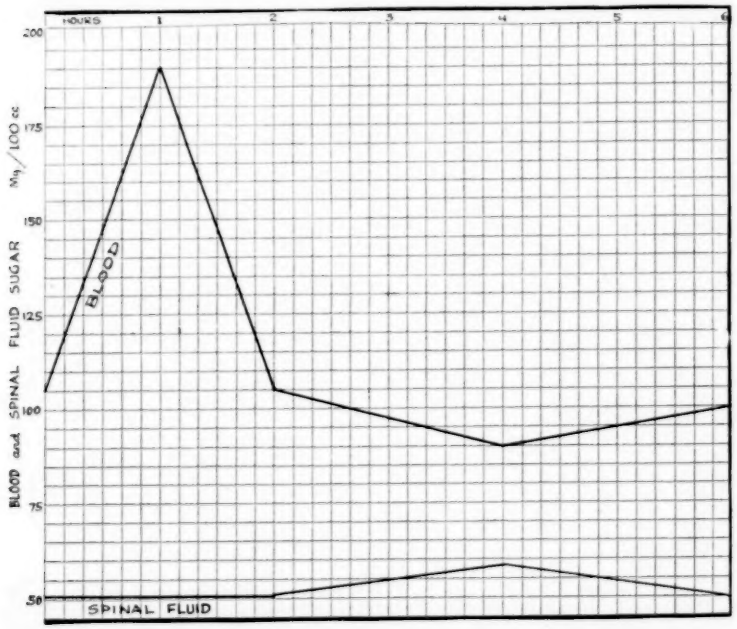

Chart 5.—Blood and spinal fluid sugars before and after glucose tolerance tests.

the cerebrospinal fluid, but the relation to the blood sugar was not determined.

High spinal fluid sugars have been reported in several other conditions. In 1920, Fiessinger and Janet [19] reported three cases, one of diffuse sarcomatosis with sarcoma in the basilar process of the sphenoid pressing on the mesencephalon, with sugar contents of the spinal fluid of 103 and 293; one of meningeal hemorrhage, with sugar contents of the spinal fluid of 95 and 115, which is about that of normal blood, due

19. Fiessinger, N., and Janet: Bull. et mém. Soc. méd. d. hôp. de Paris **45**:145, 1920.

to the amount of blood in the fluid from the hemorrhage; and one of terminal meningeal miliary tubercles (not tuberculous meningitis) with sugar content of the spinal fluid, 180, without glycosuria. In 1912, Achard and Rouillard [20] reported a case of mesencephalic syphilis simulating encephalitis with cerebrospinal sugar of 75 and 70.

A number of cases of brain tumor with high cerebrospinal fluid sugar have been reported in recent literature. In 1922, Thalheimer and Updegraff [10] reported such a case with a cerebrospinal fluid sugar content of 179. In 1923, Wilcox and Lyttle [11] reported a case of glioma of the cerebellum with a blood sugar of 93 and a cerebrospinal fluid sugar of 93.

CONCLUSIONS

To be of value in determining whether or not a spinal fluid sugar is high or low, the fluid must be taken after a night's fasting and the sugar content compared to that of the blood taken at the same time.

Our figures would indicate that the following conclusions might be drawn:

1. The sugar content of the cerebrospinal fluid is not constant in the same individual.

2. There is no level, within reasonable limits, which might be considered normal for different individuals.

3. There is a definite relationship between the sugar content of the cerebrospinal fluid and of the blood, which may be expressed as the percental relation of the sugar content of the cerebrospinal fluid to the sugar content of the blood. This figure lies with fair constancy within the limits of 45 and 65 per cent.

4. The ingestion of carbohydrate in sufficient quantities causes a definite and constant rise in the sugar content of the cerebrospinal fluid and disturbs the usual relationship between the sugar content of the cerebrospinal fluid and that of the blood.

5. Meningitis, whether tuberculous, staphylococcus or meningococcus, frequently gives a low sugar content of the cerebrospinal fluid, both as to actual milligrams per hundred cubic centimeters and in relation to that of the blood.

The literature shows a high sugar content of the cerebrospinal fluid in relation to the sugar content of the blood in cases of encephalitis.

Untreated cases of early cerebrospinal syphilis give a low actual and relative sugar content of the cerebrospinal fluid. Under treatment, this figure returns to normal.

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20. Achard, C., and Rouillard, J.: Bull. et mém. soc. méd. d. hôp. de Paris **45**:130 (Feb. 11) 1921.

When considering the fact that the sugar content of the spinal fluid is lowered with a fair degree of constancy in cases of tuberculous, meningococcus and staphylococcus meningitis, one must remember that a low figure after intraspinal administration of antimeningococcus serum is of no diagnostic value.

VITAL CAPACITY AS A FUNCTIONAL TEST IN HEART DISEASE*

THOMAS ZISKIN, M.D.
MINNEAPOLIS

To devise a simple test for estimating the functional capacity of the heart has been the aim of many investigators for several years. Many tests were advanced, most of them based primarily on the response of the heart to exercise. The majority of these tests have proved of very little value and are not being used today. Within the past decade, the study of the vital capacity of the lungs as a functional test in heart disease has gained favor with many clinicians, and favorable reports on the use of this test have been made by Peabody and Wentworth,[1] Ulrich and Nathanson[2] and others. Peabody and Wentworth[1] state that there is a definite relation between the vital capacity and the tendency to dyspnea, and have classified cardiac patients into four classes according to the heart's efficiency.

Patients with a vital capacity of 90 per cent. or more of the normal standard were able to carry on their work with very little dyspnea. Patients with a vital capacity of from 70 to 90 per cent. of normal became dyspneic on unusual exertion. Patients with a vital capacity of from 40 to 70 per cent. of normal became dyspneic on moderate or slight exertion and those with a vital capacity of less than 40 per cent. of the normal are decompensated patients and usually confined to bed.

Opitz,[3] while admitting that a marked decrease in vital capacity signifies cardiac decompensation and that the percentage indicating its reduction may be employed as a measure of failure to compensate, questions greatly the assertion that the vital capacity portrays the condition of the patient more plastically than the blood pressure and pulse. He emphasizes also that the vital capacity does not change materially in those cardiac patients whose compensation is adequate.

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* From the Department of Medicine, University of Minnesota Medical School and the Cardiac Section, United States Veterans' Bureau Clinic, District 10.

* Read before the combined staffs of Lymanhurst Hospital and Parkview Sanitarium, June 24, 1924.

1. Peabody, F. W., and Wentworth, J. A.: Clinical Studies of the Respiration. IV. The Vital Capacity and Its Relation to Dyspnea, Arch. Int. Med. **20**:443 (Sept.) 1917.

2. Ulrich, H. L., and Nathanson, M. H.: The Vital Capacity of the Lungs in Cardiac Disease, Minnesota Med. **4**:721 (Dec.) 1921.

3. Burton-Opitz, Russell: Vital Capacity of "Cardiacs," J. A. M. A. **78**:1686 (June 3) 1922.

The present study was undertaken for the purpose of adding what little I may to a better understanding of the relationship between vital capacity and cardiac efficiency. The observations were made on a group of 207 cardiac patients at the U. S. Veterans' Bureau clinic. A thorough clinical study was made of each case, and only those cases were selected which had no complications outside the circulatory system that would in any way affect the vital capacity. The functional capacity of the heart was determined by a study of the history, symptoms,

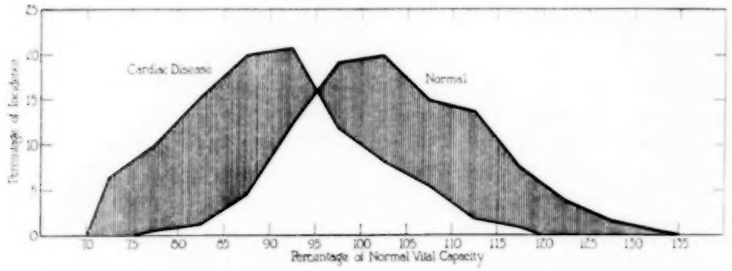

Chart 1.—Vital capacity in Class 2*a* patients (111 cases). Organic; able to carry on, with slightly diminished physical activity.

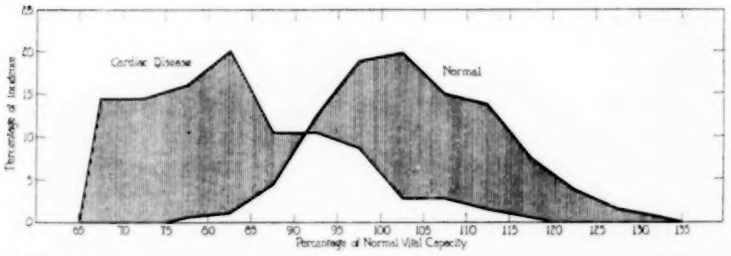

Chart 2.—Vital capacity in Class 2*b* patients (69 cases). Organic; able to carry on, with greatly diminished physical activity.

physical signs and the response to exercise, and the patients were then placed into one of five groups according to the classification of the Association of Cardiac Clinics.

Class 1.—Organic (able to carry on usual physical activity).

Class 2.—Organic (able to carry on, *a*, slightly diminished physical activity; *b*, greatly diminished physical activity).

Class 3.—Organic (unequal to any physical activity).

Class 4.—Possible heart disease (doubtful murmurs, mainly functional, possibly organic).

Class 5.—Potential (predisposing history of rheumatism, tonsillitis, etc.). The vital capacity was calculated by means of West's [4] formula (body surface in square meters times, 2,500). The surface area was determined by the linear formula of DuBois and DuBois.[5] There were six cases in Class 1, that is, patients who never had any symptoms of heart disease and in whom the condition was discovered only during a routine examination. The vital capacity in this group ranged from 100 per cent. to 123 per cent. of the normal. The majority of the patients were either in Class *2 a* or Class *2 b*. There was also a small group of twenty cases in Class 4. This group included the cardiac neuroses and other functional cardiac conditions. The distribution of the vital capacities in each of these groups is shown in Table 1 and also by curves in comparison with the normal curve in Charts 1, 2 and 3.

The normal curve used in these figures was prepared by Shepard and Myers [6] from a study of over 3,500 male university students. Their vital capacity determinations were made by all the various methods in use and the average used as the normal.

TABLE 1.—*Distribution of Vital Capacity in Cardiac Disease*

Percentage Normal Vital Capacity	Class 2*a*		Class 2*b*		Class 4	
	Cases	Per Cent.	Cases	Per Cent.	Cases	Per Cent.
Below 70	..	....	10	14.3	..	....
71– 75	7	6.3	10	14.3	1	5.0
76– 80	11	10.0	11	15.7	2	10.0
81– 85	17	15.3	14	20.0	0	0.0
86– 90	22	20.0	7	10.0	1	5.0
91– 95	23	20.7	7	10.0	5	25.0
96–100	13	11.7	6	8.6	6	30.0
101–105	9	8.1	2	2.9	2	10.0
106–110	6	5.4	2	2.9	1	5.0
111–115	2	1.8	1	1.4	1	5.0
116–120	1	0.9	0	0.0	1	5.0
Total	111	100.0	70	100.0	20	100.0

It will be seen that in Class *2 a*, patients who are able to carry on with slightly diminished physical activity, the average vital capacity of the group is between 86 and 90 per cent. of normal; while in Class *2 b*, patients who are able to carry on with greatly diminished physical activity, the average is between 81 and 85 per cent. of normal. In Class 4, patients who have no organic condition, the average vital capacity is between 96 and 100 per cent. of the normal. A study of

4. West, H. F.: Clinical Studies on Respiration. A Comparison of Various Standards for Normal Vital Capacity of the Lungs, Arch. Int. Med. **25**:306 (March) 1920.

5. DuBois, D., and DuBois, E. F.: A Formula to Estimate Approximate Surface Area if Height and Weight be Known, Arch. Int. Med. **17**:863 (June) 1916.

6. Shepard, W. P., and Myers, J. A.: Personal communication (to be published).

the curves in these various groups shows that the distribution follows very close to the normal curve, although there is a lowering and shifting to the left of the curves in Class 2 *a* and Class 2 *b* and slightly in Class 4. There is very little difference, however, between the curves of Class 2 *a* and Class 2 *b*. These results tend to show that while the vital capacity is usually reduced in the majority of ambulant cardiac patients, the range of distribution is very variable and cannot be limited by any class or group. The difference between the group which was

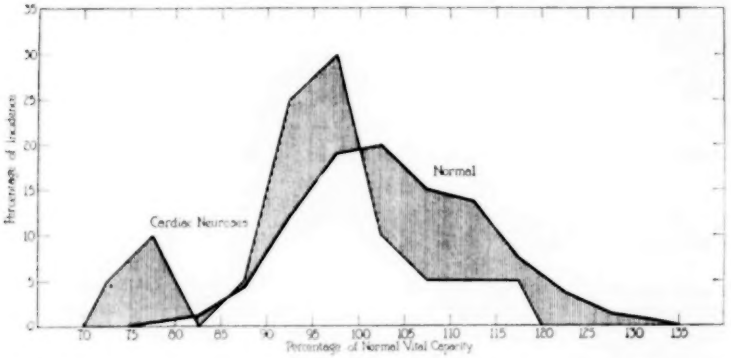

Chart 3.—Vital capacity in Class 4 patients, cardiac neuroses (20 cases).

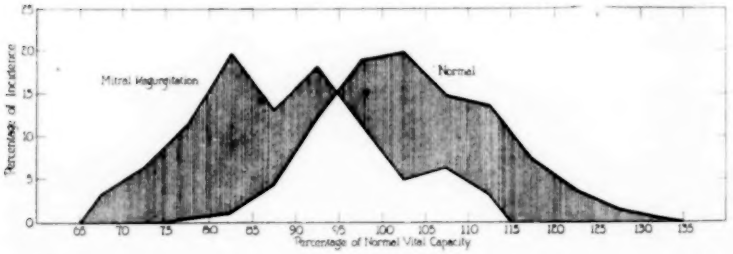

Chart 4.—Vital capacity in chronic valvular disease with mitral regurgitation (60 cases).

able to carry on with slightly diminished activity and the group which was able to carry on only with greatly diminished activity is not marked, although the latter group does show a greater number with lower vital capacities.

A study of this series of cases was made also with a view to determine whether there is any relation between the type of lesion and the vital capacity. The results are shown in Table 2 and Charts 4 to 8, inclusive.

The average vital capacity is lowest in the group in which more than one valve is affected, being from 76 to 80 per cent. of normal. In mitral stenosis the average was between 81 and 85 per cent. of normal, while in mitral regurgitation, aortic regurgitation and the myocardial insufficiencies the average vital capacity was the same, being between 86 and 90 per cent. of normal. In the patients affected with aortic regurgitation there was a tendency for the distribution to be within a prescribed limit, the majority falling within 86 and 100 per cent. of normal. In the other groups, the tendency was to follow the normal curve, although in each of them the abnormal curve is lowered and shifted to the left. These results agree with the findings of Peabody and Wentworth,[1] that the vital capacity tends to be lower in mitral disease than in aortic disease and also that the vital capacity depends more on the severity of the lesion than on the type of lesion.

TABLE 2.—*Distribution of Vital Capacity in Various Types of Heart Disease*

Percentage Normal Vital Capacity	Mitral Regurgitation		Mitral Stenosis		Aortic Regurgitation		Aortic and Mitral Disease		Myocardial Conditions	
	Cases	Per Cent.	Cases	Per Cent.	Cases	Per Cent.	Cases	Per Cent.	Cases	Per Cent.
Below 70.....	2	3.3	2	6.3	..	..	3	15.0	2	4.3
71–75.....	4	6.6	2	6.3	1	5.0	4	20.0	5	10.6
76–80.....	7	11.6	4	12.5	1	5.0	5	25.0	5	10.6
81–85.....	12	20.0	8	25.0	0	0.0	2	10.0	8	17.0
86–90.....	8	13.3	5	15.6	8	40.0	0	0.0	8	17.0
91–95.....	11	18.3	3	9.4	2	10.0	3	15.0	11	23.4
96–100.....	7	11.6	4	12.5	4	20.0	2	10.0	2	4.3
101–105.....	3	5.0	3	9.4	2	10.0	1	5.0	2	4.3
106–110.....	4	6.6	1	3.1	1	5.0	0	0.0	2	4.3
111–115.....	2	3.3	0	0.0	1	5.0	0	0.0	1	2.1
116–120.....	0	0.0	0	0.0	0	0.0	0	0.0	1	2.1
Total.....	60	100.0	32	100.0	20	100.0	20	100.0	47	100.0

COMMENT

That the vital capacity in heart disease bears a relationship to the symptom dyspnea, there is no doubt, but that the relationship is definite and the reduction in vital capacity parallels the reduction in cardiac efficiency is not shown by the results obtained in this group of cases. Several other factors must be taken into consideration in determining the cause of reduced vital capacity and its relation to cardiac efficiency. The vasomotor system is a great factor here, as it is in all tests for cardiac efficiency. Mechanical factors which interfere with the movements of the chest wall, such as rigidity of the bony framework, ankylosis of the costal joints, weakness of the intercostal muscles, and so forth, must be considered. Conditions within the chest itself, such as pleural effusion, emphysema and cardiac enlargement may influence the vital capacity, also conditions which cause increased abdominal pressure, such as enlarged liver, abdominal tumors and ascites.

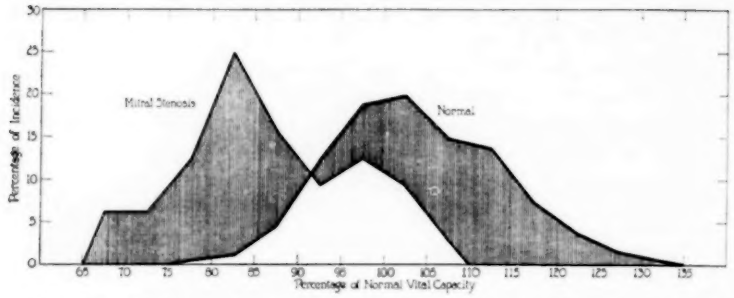

Chart 5.—Vital capacity in chronic valvular disease with mitral stenosis (32 cases).

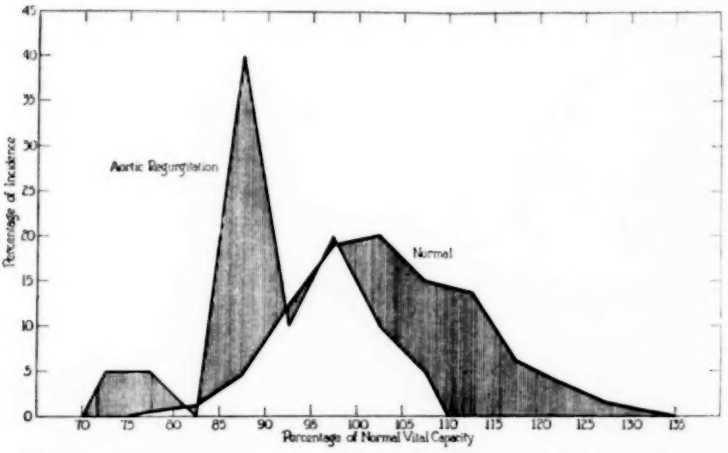

Chart 6.—Vital capacity in chronic valvular disease with aortic regurgitation (20 cases).

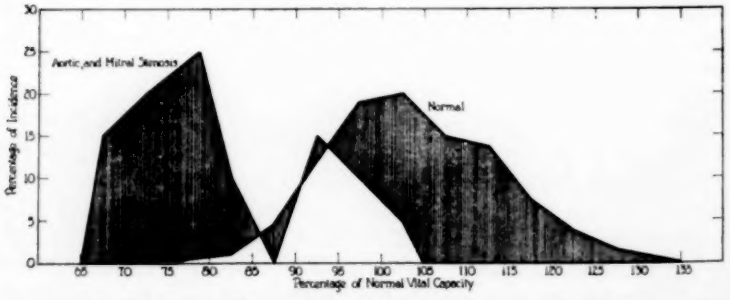

Chart 7.—Vital capacity in chronic valvular disease with aortic regurgitation and mitral disease (20 cases).

The primary cause of dyspnea is best explained by Siebeck,[7] who states that it is due to an engorgement of the capillaries of the lung alveoli, which in turn causes a distention of the alveolar walls with an increase of fibrous tissue and a resultant inelasticity of the alveolar walls. Pathologic examination of the lungs of passive congestion bears this out. Dyspnea, therefore, is due primarily to an alveolar insufficiency. This insufficiency may vary in different persons with the same amount of alveolar tension, and the same amount of alveolar insufficiency may produce varying degrees of symptomatology in different persons, just as an increase in arterial tension does not affect all hearts in the same way. This may in a measure explain the variability of the vital capacity readings in each clinical group. Also, as the range of the normal vital capacity varies from 75 to 135 per cent. of the theoretic

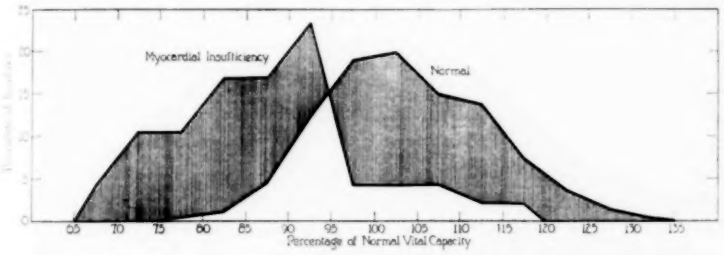

Chart 8.—Vital capacity in cardiac disease with myocardial insufficiency (47 cases).

100 per cent., so the range of the vital capacity in this group of cases, although lowered, varies from 60 to 120 per cent. of the theoretic 100 per cent. Therefore, a vital capacity reading in any given heart condition, unless it was very low, would not give us any conclusive information, as there is no way of determining its relation to the normal curve. A subject may have a vital capacity of 100 per cent. and still be greatly reduced when compared to a normal person with 135 per cent.

SUMMARY

1. Vital capacity is of value in the study of heart conditions.

2. There is no definite relationship between the vital capacity and cardiac efficiency in ambulant cardiac patients.

3. There is no definite relationship between the vital capacity and the type of heart lesion.

7. Siebeck, R.: Ueber die Beeinflussing der Atemmeckanick durch Krankhafte Zustände des Respiration und Kreislaufapparetes, Deutsch. Arch. f. klin. Med. **100**:204, 1910.

NOTES ON THE THERAPEUTIC VALUE OF PNEUMOCOCCUS ANTIBODY SOLUTION SUBCUTANEOUSLY ADMINISTERED IN LOBAR PNEUMONIA *

WADE W. OLIVER, M.D.
AND
E. A. STOLLER, M.D.
BROOKLYN

The work reported in this article is concerned with our findings at Long Island College Hospital, during the fall, winter and spring of 1923-1924, as a part of a clinical experiment with the subcutaneous administration of pneumococcus antibody solution pursued under the supervision of the influenza commission in the cities of New York, Boston, Cincinnati and Chicago. It seemed desirable to study the effect of antibody solution administered subcutaneously, largely because previous workers seemed to be agreed that the reactions following intravenous inoculation of antibody solution are often severe and sometimes actually dangerous to the patient. In the interests of uniformity and in order to provide comparable results, the experimental clinical work was pursued in accordance with the following plan outlined by the influenza commission.

SELECTION OF CASES

1. Every case giving a typical history of chill, fever, pain in the side and cough with rusty sputum, together with typical physical signs of consolidation, as indicated by dulness, bronchial breathing and bronchophony, is included. The area of consolidation need not be extensive.

2. Included also are cases without a typical history but with frank physical signs of consolidation, when there is a reasonable certainty that these signs are not caused by infarct, tuberculosis, tumor, or other organic disease not lobar pneumonia.

3. Cases with typical history and symptoms of lobar pneumonia, even if physical findings are negative, provided a definite shadow is demonstrated by roentgen-ray examination, are included.

4. Included also are cases in which the history and physical findings are suggestive but not typical of lobar pneumonia, provided the patient's sputum shows pneumococcus Types I, II and III.

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* From the department of bacteriology, Hoagland Laboratory, and the department of medicine, Long Island College Hospital.

PLAN OF PROCEDURE AS OUTLINED BY THE INFLUENZA COMMISSION

1. In every hospital cooperating in this study, there should be some one person responsible for, and having general supervision of, the experiment.

2. Each ward will be considered an experimental unit. Every case of lobar pneumonia admitted to a particular ward will be numbered consecutively. First case, 1; second case, 2; and so on.

3. Every case receiving an even number shall have the antibody treatment. The odd numbered cases will not receive antibody treatment, but in other respects will be handled like the antibody cases. In the case of our particular work at Long Island College Hospital, the foregoing plan was deviated from to the extent of administering antibody solution to one half of the Type I pneumococcus pneumonia patients in the series, and to certain of the remainder of the Type I pneumonia patients administering Type I pneumococcus antiserum. By this means, it was hoped to obtain some data on the comparative value of antibody solution and antiserum in Type I infections. Also, on two occasions, when the supply of antibody solution was temporarily exhausted, the sequence was broken to the extent that an even numbered case failed to receive antibody solution, and vice versa.

4. In order to minimize the personal equation in the diagnosis and effect of treatment, it is necessary that both the antibody and control cases come under the direct observation of the same person, in each experimental unit or ward.

TREATMENT

1. Antibody solution will be administered subcutaneously in the flank or anterior abdominal wall. The first injection will be given as soon as the clinical diagnosis of lobar pneumonia has been made. In certain of the cases in our series, subcutaneous administration of antibody solution subpectorally was resorted to.

2. The initial dose of the antibody solution will be from 200 to 300 c.c. depending on the severity of the case. The second dose (from 200 to 300 c.c.) will be administered from eight to twelve hours after the first dose. The amount of subsequent dosage will depend on the severity of the infection and the result produced by the first two injections.

3. In general, it may be said that in very severe cases from 200 to 300 c.c. should be given three times in the first twenty-four hours; during the second twenty-four hours, from 200 to 300 c.c. twice a day. Smaller doses (from 100 to 150 c.c.) may be used after the first two

injections, if the patient has responded well, or if the infection is not severe. Treatment should be continued until the temperature reaches from 99 to 100 F. and remains there.

NUMBER OF CASES STUDIED

The series on which this report is based consisted of forty-nine cases of pneumonia of which twenty-six were controls and twenty-three were treated with antibody solution. Alternate patients were given antibody solution, as far as this was possible. There were more controls than antibody cases because on two occasions our supply of antibody solution was exhausted and shipment was unavoidably delayed. However, we

TABLE 1.—*Bacteriologic Classification of Cases by Sputum Typing*

Micro-organism	Number of Cases	Percentage Incidence
Pneumococcus Type I	15	30.61
Pneumococcus Type II	5	10.2
Pneumococcus Type III	2	4.08
Pneumococcus Type IV	24	48.97
Streptococcus	2	4.08
Undetermined	1	2.04

TABLE 2.—*Results of Blood Cultures*

Micro-organism	Positive	Negative	Not Taken	Percentage of Positives
Pneumococcus Type I	6 (4 cases)	9 (8 cases)	3	40
Pneumococcus Type II	—	4	1	0
Pneumococcus Type III	—	2	—	0
Pneumococcus Type IV	5 (4 cases)	18 (16 cases)	4	21.79
Streptococcus hemolyticus	1 (sputum Type III pneumococcus)	1	1	50
Undetermined	—	1	—	0

would emphasize that in the series of cases which comprise the experiment, there was nothing even remotely resembling a selection of cases.

We are perfectly frank in admitting that the series on which the report is based is small in number. However, the fact that the work was quite rigorously controlled and that there was no selection of cases makes the results of comparative value.

BACTERIOLOGIC CLASSIFICATION OF CASES

The methods employed in determining the specific type of pneumococcus responsible for the infection in each case were: (1) a rapid method;[1] (2) the Mouse method; (3) the Avery method, and (4) blood cultures whenever possible. The diagnostic serums used for typing were supplied by the New York state board of health.

1. Oliver, W. W.: J. Infect. Dis. **27**:310 (Oct.) 1920; ibid. **29**:518 (Nov.) 1921.

Two rather unusual cases, from the bacteriologic standpoint, were encountered in the series. The first case was one of lobar pneumonia, in which the sputum contained a Type III pneumococcus, as demonstrated by the Mouse method, the Avery method, and a rapid method. On the same day that the sputum typing was performed, a blood culture was made which, on twenty-four hours incubation at 37.5 C., revealed a hemolytic streptococcus in pure culture. The second was a control case untreated with specific therapy. He was an East Indian, aged 25, who was admitted to the hospital on the fourth day of his illness and died on the seventeenth day. The clinical diagnosis was a "massive bronchopneumonia." On the fifth day of his illness, a sputum typing, done by the Mouse method and the Avery method, revealed a Type II regular pneumococcus. A blood culture, taken on the same day, remained sterile on ten days incubation at 37.5 C. The seventeenth day of the disease, another blood culture was taken which revealed over 1,000 colonies per cubic centimeter of a Type I pneumococcus in pure culture. A postmortem lung culture was also positive for Type I pneumococcus in pure culture.

NATURE OF ANTIBODY SOLUTION

The pneumococcus antibody solution employed in the following experiments was prepared by F. M. Huntoon,[2] and was supplied by the Mulford Laboratories. Huntoon's method of dissociation of antibody from its antigen represents an extension and refinement of a method previously described by Gay and Chickering.[3] To a mixture of Type I, Type II and Type III pneumococcus antiserum is added an equal volume of a heavy suspension of living pneumococci, Types I, II and III. This mixture is allowed to stand for one hour at 37.5 C., or for twelve hours at 20 C.; this amount of time allows for a union of specific antibodies to specific antigens. The pneumococci are then thrown down with a centrifuge, and the micro-organisms are washed with physiologic sodium chlorid solution, at almost the freezing point, in order to remove traces of horse serum. The washed sediment is next suspended in salt solution containing 0.25 per cent. sodium bicarbonate and heated from thirty minutes to one hour at 55 C. By such treatment, the antibodies are dissociated from the antigen-antibody complex. The mixture is then centrifugated, and the removed supernatant fluid, which contains the antibodies, is chilled, recentrifugated and finally filtered through a filter candle. The final solution is almost completely protein free, and may contain as low as 0.035 mg. of nitrogen per cubic centimeter.

2. Huntoon, F. M.: J. Immunol. **6**:117 (March) 1921.
3. Gay and Chickering: J. Exper. Med. **21**:389, 1915.

METHOD OF ADMINISTRATION OF ANTIBODY SOLUTION

As the previous intravenous use of pneumococcus antibody solution had been attended by severe reactions which were occasionally harmful and, in a few instances, fatal, it became of more than academic interest to find a new method for its administration, if antibody solution was to become a therapeutic agent of general, practical clinical value. For this purpose, the subcutaneous route was chosen.

The first site selected was the abdominal skin, but it was soon discovered that it took almost an hour to introduce from 150 to 200 c.c. by the gravity method, even if the direction of the needle was changed repeatedly. It was then decided to try the skin of the lower axillary region, and this gave somewhat better results, because, as a rule, the skin in this area was more lax and the subcutaneous tissues permitted of greater distention by the fluid. In a further attempt to facilitate the administration, subpectoral injections were employed. This last method seemed to be the most satisfactory because the operation took less time, thereby causing less discomfort to the patient. Moreover, so far as could be determined, the absorption rate was not materially affected, because there was no increase in the incidence of reactions of any sort.

The actual technic of the injection was as follows: The skin area chosen was carefully cleaned with 3.5 per cent. tincture of iodin. With a small hypodermic needle, from 1 to 2 per cent. procain solution was injected intradermally until a raised area about the size of a 10 cent piece was produced. When successfully introduced, the procain gave rise to a very white area in which the hair follicles stood out prominently, so that the anesthetized area gave the appearance of a porous plaster. A needle, connected by tubing with a graduated cylinder which contained the antibody solution, was then introduced through the anesthetized area into the subcutaneous tissues, and the solution was allowed to flow in by the gravity method. On the average, twenty minutes sufficed for the subpectoral injection of 200 c.c. of antibody solution.

The following lot numbers of antibody solution were employed during the course of our experiment: 61269, 61487, 60785, 62179, 62477, 22179, 63339, 63310, 63737, 63898 and 64838.

The largest amount of antibody solution employed in any one case in our series was 3,400 c.c., of which the initial 1,900 c.c. was polyvalent and the remainder univalent Type I solution, and this was given in thirteen doses eight hours apart, in a case of Type I pneumococcus infection, with no apparent effect on the clinical course. In another case, of Type IV infection, 2,350 c.c. of polyvalent antibody solution was given in nine doses eight hours apart. The disease lasted seven days and terminated by lysis. Extension to another lobe occurred on the fifth

day. In view of the fact that these massive doses apparently did not materially influence the course of the disease, it was arbitrarily decided to discontinue antibody treatment in any given case after 1,000 c.c. had been given. The smallest amount of antibody solution used was 350 c.c., and this case (Case 2) gave the most spectacular result in our series (Chart 6).

REACTIONS FOLLOWING SUBCUTANEOUS ADMINISTRATION OF ANTIBODY SOLUTION

From the beginning, it was felt that the antibody solution contained an irritant of some sort, because the patients invariably complained when the site of an injection was touched. This tenderness persisted for two or three days and was often very acute.

The incidence of chills or temperature reactions is apparently greatly reduced when the antibody solution is given subcutaneously, rather than intravenously. Cecil and Larsen,[4] in commenting on the effect of intravenously administered antibody solution, say, "The reactions are often very uncomfortable and in certain cases are actually injurious to the patient." Conner,[5] likewise, says of the intravenous administration of antibody solution, "The method has one serious drawback in that the immediate, or so-called thermal, reaction is sometimes very severe and may even result in death." Cecil and Larsen and Conner report that temperatures of 106 F., from twenty to forty-five minutes after the initial injection, are not uncommon.

In our series of twenty-three patients to whom antibody solution was administered subcutaneously, only two patients exhibited a chill and temperature rise following injection. In Case 2, a Type II pneumococcus infection, 200 c.c. of antibody solution were given as an initial injection at 3 p. m. Nine hours later, 150 c.c. of antibody solution was injected. One-half hour later, the patient had a severe chill which lasted for twelve minutes. Fifteen minutes after the chill had stopped, the temperature was 106.2 F. (rectal) as compared with 101.6 (rectal) before the second injection was given. In Case 12, a Type I pneumococcus infection, one-half hour after the thirteenth dose, which made a total of 3,400 c.c. of antibody solution which had been administered, there was a chill lasting thirty-eight minutes, and the temperature rose from 101 (rectal) to 105.8, followed by a sharp fall in the temperature to normal.

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4. Cecil, R. L., and Larsen, N. P.: Clinical and Bacteriologic Study of 1,000 Cases of Lobar Pneumonia, J. A. M. A. **79**:343 (July 29) 1922.

5. Conner, L. A.: Am. J. M. Sc. **164**:832 (Dec.) 1922.

EFFECT OF ANTIBODY SOLUTION ON STERILIZING THE BLOOD STREAM

In one out of the four cases of Type I infection in which blood cultures were positive, a striking example of the failure of antibody solution, when given subcutaneously, to sterilize the blood stream was brought out. This was Case 4, a Type I pneumonia patient, admitted on the third day of the disease. From the fifth to the eighth day of the disease, inclusive, he received 1,350 c.c. of antibody solution. The fifth day of the disease, a blood culture revealed 100 colonies of Type I pneumococcus per cubic centimeter. The seventh day, the colony count was 50 per cubic centimeter of blood. The twelfth day, three days before death, there were over 500 colonies of Type I pneumococcus per cubic centimeter of circulating blood. A second patient, Case 37, with Type IV pneumococcus infection, was admitted on the third day of the disease. Antibody solution treatment was begun on admission and

TABLE 3.—*Complications in Antibody Treated and Control Cases*

Type of Compilation	Antibody Series	Control Series
Extension	5	4
Pleural effusion	0	1
Otitis media	2	1
Cellulitis	1	0
Lung abscess	0	1
Phlebitis	0	1
Abscess of arm	1	0
Ischiorectal abscess	1	0
Urticaria	1 (on 11th day)	1 (Type 1 serum case)
Total	11	9

carried on through the fifth day of the disease, the total amount of antibody solution which he received being 1,000 c.c. The fourth day of his illness, a blood culture was sterile. The eighth day of the disease, a blood culture revealed one colony per cubic centimeter of blood of a Type IV pneumococcus. This lack of result in the case of Type IV infection was rather to be expected from the fact that antibody solution contains only protective antibodies against the fixed pneumococcus types, combined with the experimentally demonstrated fact that only against a limited number of Type IV pneumococcus strains does antibody solution exhibit any protective action.

COMPLICATIONS

Table 3 gives a list of the complications which developed in the antibody treated cases and the control cases.

In this connection, we desire to describe in detail the complication that arose in Case 4. The patient had received three injections of antibody solution into the left axilla, three injections into the right axilla, and

two injections under the abdominal skin. Two days after the last injection, the entire right side of the patient, from the apex of the axilla to a point about one hand's breadth above the right iliac crest, was reddened, indurated, tender and hot, and could be made to pit on pressure. Hot wet compresses were applied, but no fluctuation occurred, possibly because he did not live long enough. The process had all the outward appearance of a cellulitis. No doubt, part of this reaction could be ascribed to the tenderness and pain following the subcutaneous injection of antibody solution that was noted in some degree in every case that received the antibody treatment.

TABLE 4.—*Mortality in Antibody Treated and Control Cases*

	Antibody		Controls		Total	
	Cases	Deaths, per Cent.	Cases	Deaths, per Cent.	Cases	Deaths, per Cent.
Type I	7	28.57	8	25.0	15	26.66
Type II	4	0.0	1	0.0	5	0.0
Type III	2	50.0	0	.....	2	50.0
Type IV	10	10.0	14	21.42	24	16.66
Streptococcus	..	.....	1	.....	1	.....
Hemolytic streptococcus	..	.....	1	.....	1	.....
Undetermined	..	.....	1	100.0	1	100.0
Total	23	17.39	26	23.7	49	20.408
Average day of disease on which admitted	4.43		4.307			
Average age	32.869		31.23			

TABLE 5.—*Effect of Antibody Solution as Compared with Type I Pneumococcus Antiserum in Type I Pneumonia*

	Antibody	Per Cent.	Serum	Per Cent.	No Specific Treatment	Per Cent.	Total, per Cent.
Number of cases	7	....	6	.....	2	...	15
Death rate	2	28.5	0	0	2	100	26.66
Extension	2	28.5	1	16.66	1	50	20
Urticaria	...	....	1	16.66	...	...	.....
Cellulitis (from injections)	1	14.28	...	.....	...	...	.....
Ischiorectal abscess	1	14.28	...	.....	...	...	.....
Otitis media	1	14.28	...	.....	...	...	.....

EFFECT OF THE ANTIBODY SOLUTION ON THE COURSE OF THE DISEASE

In our limited series of antibody treated cases, there was no striking improvement noted from day to day even in the cases which seemed to be benefited. With the exception of Case 2, a Type II pneumococcus infection, in which a crisis was obtained after two injections of antibody solution, it was impossible to notice any marked signs of subjective clinical improvement. Notes on Case 31, a Type I pneumococcus infection, show that, after the first two doses of antibody solution, the pain in the chest was improved. While the treatment was going on, the patient was sufficiently comfortable to read the newspaper, although the temper-

ature rate and the respiration rate were not influenced and the disease apparently ran its self limited course, with a pseudocrisis on the seventh day and a real crisis on the eighth day. Even in the cases that were interpreted as improved, the pain caused by the injections usually over-

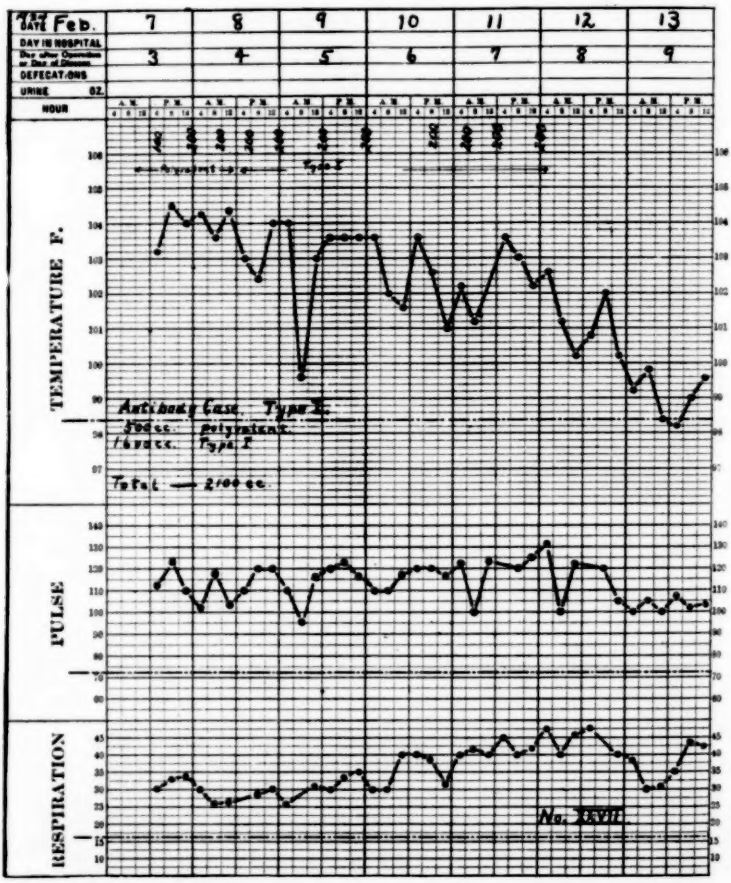

Fig. 1.—Temperature, pulse and respiration in Case 27.

shadowed any except the most striking clinical changes. In Case 6, the patient being a chronic alcoholic with delirium, although no sudden marked drop in temperature occurred, yet the general condition, on the eighth and ninth days, was unusually good in a type of case in which the prognosis is customarily considered poor. Finally, in Case 25, a

mild Type II pneumococcus infection, between the second and the fifth day of the patient's disease, he had received 800 c.c. of antibody solution. The crisis occurred on the fifth day of the disease, and resolution set in early. We feel that the antibody solution treatment favorably

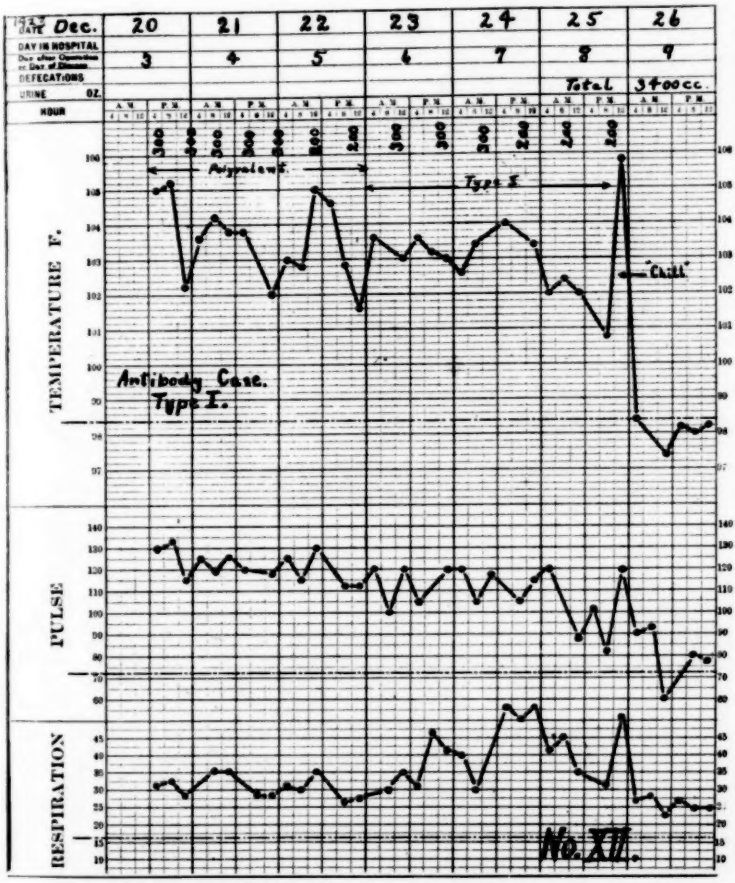

Fig. 2.—Temperature, pulse and respiration in Case 12.

influenced the course. The third day, the pain in the side was less marked, and he felt better in general.

In brief, then, in only four out of the twenty-three antibody solution treated cases was subjective improvement noted, and in three of the four cases mentioned above objective improvement also was observed.

SUMMARY OF ANTIBODY EFFECT

Subjective improvement was noted in four cases; objective improvement in three; subjective and objective improvement in three. No subjective or objective improvement was noted in nineteen cases, and

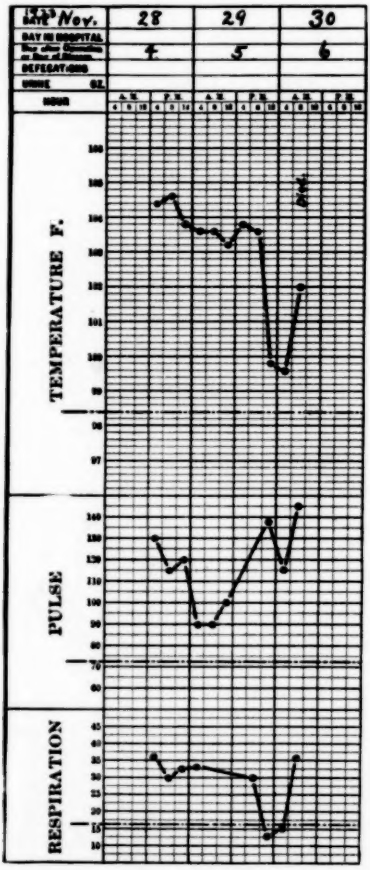

Fig. 3.—Temperature, pulse and respiration in Case 8, a control case of Type I infection.

there was marked pain at the site of the injection in twenty-three cases.

As a consideration of Table 4 will show, the striking feature is that the antibody treated cases of Type IV infection showed a little less than one-half the mortality (10 per cent.) that was exhibited by the controls

(21.42 per cent.). It also will be observed that the total mortality of the antibody treated cases plus the controls is 20.408 per cent., which is about the average mortality exhibited by pneumonia irrespective of the therapy employed.

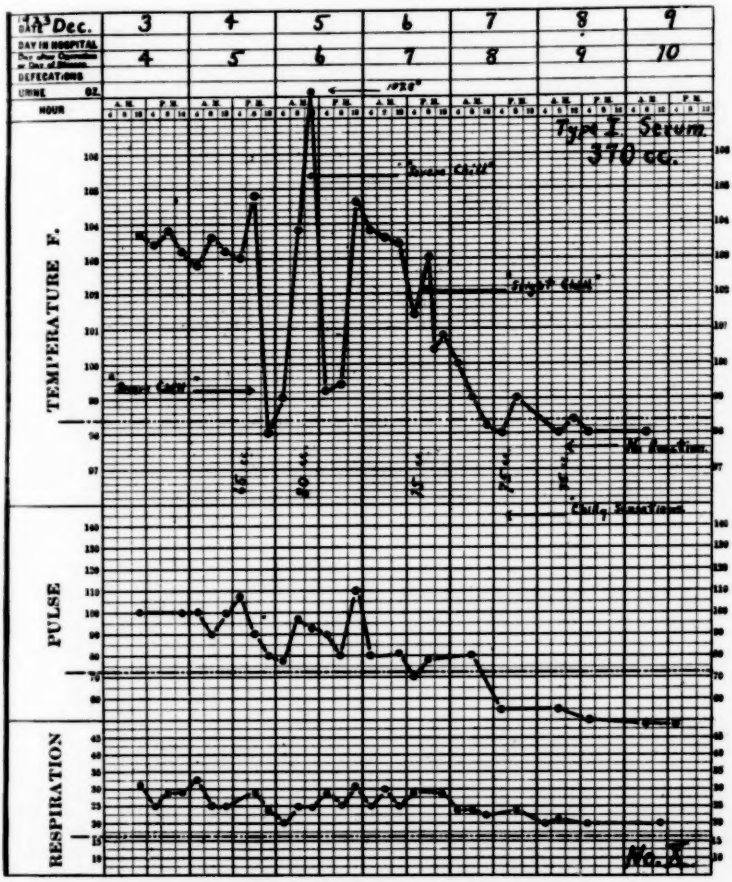

Fig. 4.—Temperature, pulse and respiration in Case 10.

CASE 27.—A man, aged 21, a Norwegian, with a pneumococcus Type I pneumonia of the left lower lobe, at entrance before the type was known, had received 500 c.c. of polyvalent antibody solution, after which he received Type I antibody solution. The fifth day, there was a pseudocrisis, and that afternoon the temperature again reached its former peak. At this time, the left lower lobe showed signs of resolution. The morning of the sixth day, the picture had entirely changed. Cyanosis was intense and breathing labored.

By this time, the left upper lobe had become solid. The eighth day, antibody treatment was discontinued because he had become progressively worse. At this time, there was some pulmonary edema. Under heavy cardiac stimulation, the blood pressure was maintained and phlebotomy was not resorted to. The crisis occurred during the night of the eighth day.

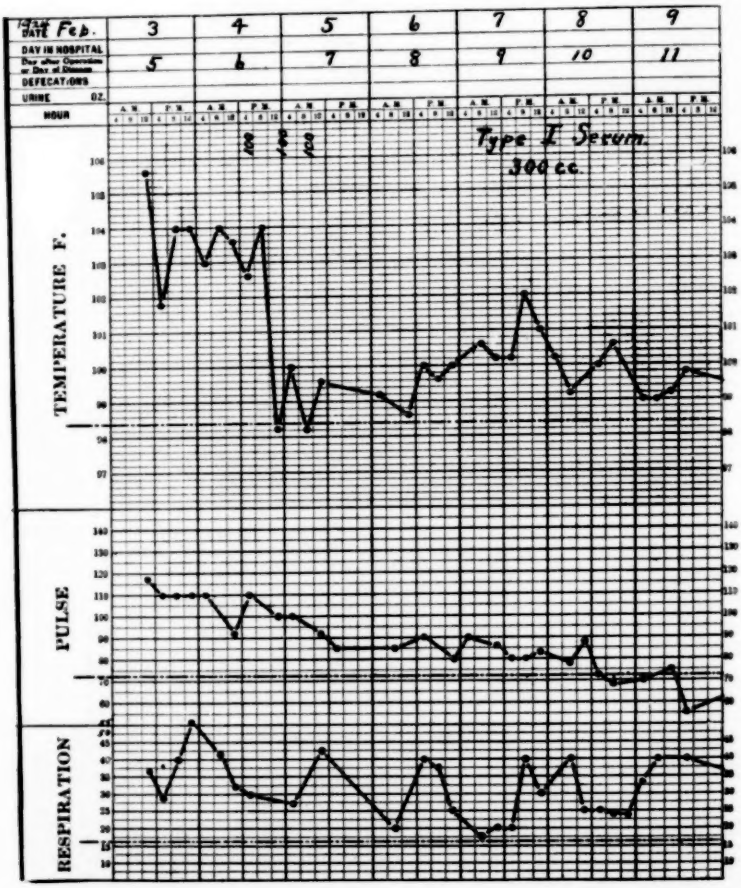

Fig. 5.—Temperature, pulse and respiration in Case 24.

In this case, in spite of vigorous antibody treatment, the symptoms were not alleviated; extension occurred, and the disease ran its course apparently uninfluenced in any way.

Case 12.—A man, aged 26, a Brazilian, with pneumococcus Type I pneumonia of the left lower lobe, after 1,900 c.c. of polyvalent antibody solution had been given, was reported to be a Type I case, and, in the succeeding injections, Type I antibody solution was used. After the first three days of antibody

treatment, the only change that could be noticed was that he was a little more comfortable and had less pleuritic pain. About one half-hour after the thirteenth dose had been given, he had a chill which lasted thirty-eight minutes, and the temperature jumped from 101 F. (rectal) to 105.8 followed by a sharp fall to 92.2, where it remained. This occurred on the ninth day of the disease.

In this case, the temperature was not brought to normal until the ninth day and then only after thirteen subcutaneous injections, totaling 3,400 c.c.

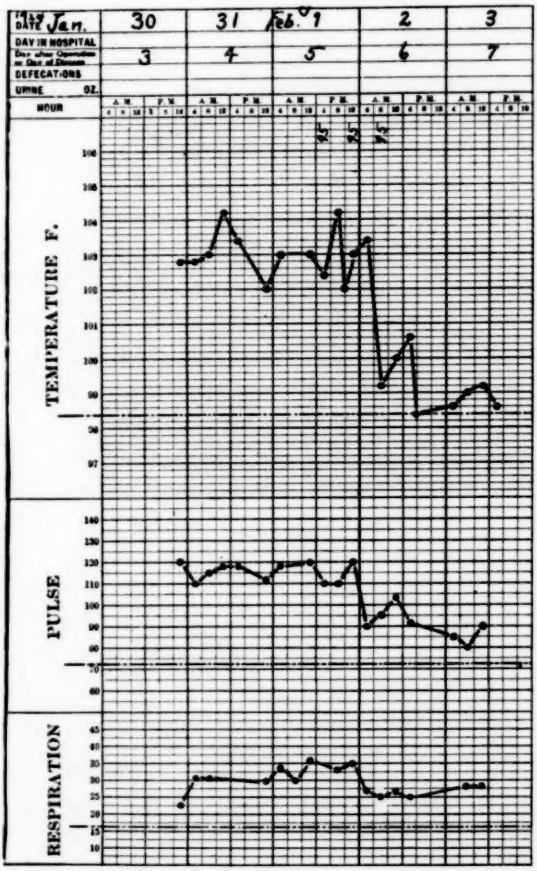

Fig. 6.—Temperature, pulse and respiration in Case 20, in which the patient was given 285 c.c. of Type I serum.

CASE 8.—A man, aged 20, a Norwegian, with a pneumococcus Type I pneumonia of the right middle and lower lobes, on examination of the heart, showed a very diffuse and powerful apex beat in the fourth and fifth interspaces. The left border measured 10 cm. and the right 4 cm. from the midsternal line. The second sound at the apex had a slapping character. There was a short systolic murmur at the apex which was poorly transmitted to the left axilla.

There was also an irregularity in rate but not in force. From the beginning, the patient showed a peculiar drowsiness and during the second twenty-four hours he was mildly delirious. About thirty-six hours after entrance, the delirium became more marked, and it was necessary to give him a narcotic, after which respirations became very slow and shallow.

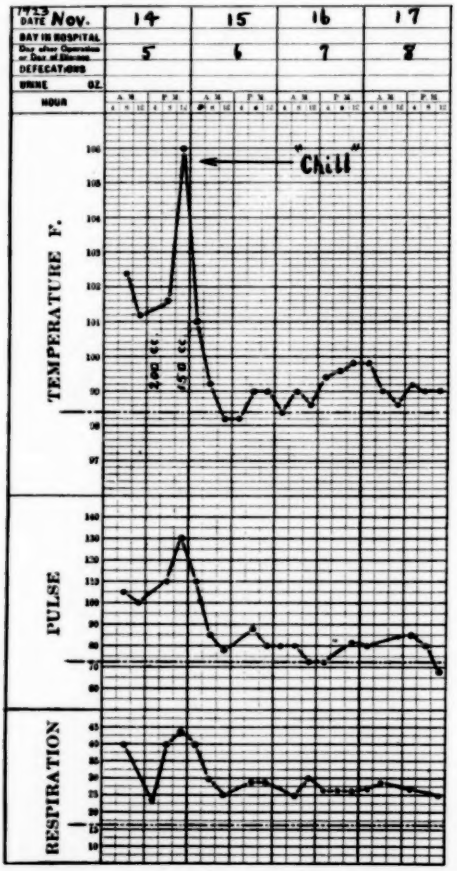

Fig. 7.—Temperature, pulse and respiration in Case 2, a Type II pneumococcus pneumonia; 350 c.c. of antibody solution (polyvalent) was given.

This case illustrates a Type I infection complicated by mitral insufficiency in which the treatment consisted only of the ordinary supportive measures. There was no history of previous cardiac or rheumatic disease.

Case 10.—A man, aged 23, a Filipino, with a Type I pneumococcus pneumonia of the left lower lobe, gave a poor response to Type I horse serum. Although treatment was begun on the fifth day, the temperature was not brought to normal until the eighth day. The first two injections were followed by such

severe chills that it was decided to procure a new lot of serum. Succeeding doses of a new lot produced only slight reactions, and the last injections produced no reactions of any kind. This patient had shown no sensitiveness to horse serum in the preliminary cutaneous tests.

CASE 24.—A man, an Italian, aged 25, with a pneumococcus Type I pneumonia of the right lower lobe, was given Type I horse serum treatment, beginning

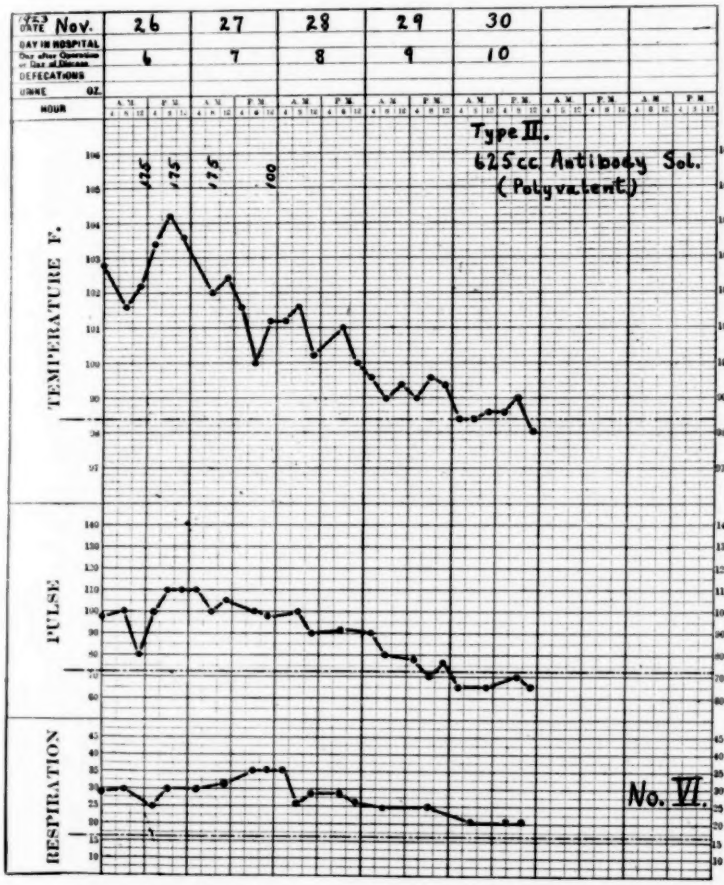

Fig. 8.—Temperature, pulse and respiration in Case 6.

on the evening of the sixth day. After the first dose of 100 c.c., given intravenously, he had rather a severe chill. By midnight, the temperature had fallen to normal by crisis. Two more doses of 100 c.c. each were given at 1 a. m. and at 9 a. m. Marked delirium set in after the first dose.

In this case, we feel that the course was favorably influenced by Type I horse serum, in spite of the fact that the patient was in wild delirium for fully forty-eight hours after the temperature had come to normal.

CASE 20.—A man, aged 21, an American, with pneumococcus Type I pneumonia of the right lower lobe, was admitted late on the third day of the disease, and serum treatment was not begun until the afternoon of the fifth day. After three doses of serum, eight hours apart, totaling 285 c.c., crisis was obtained.

In this case, we feel that the course was favorably influenced by the serum treatment.

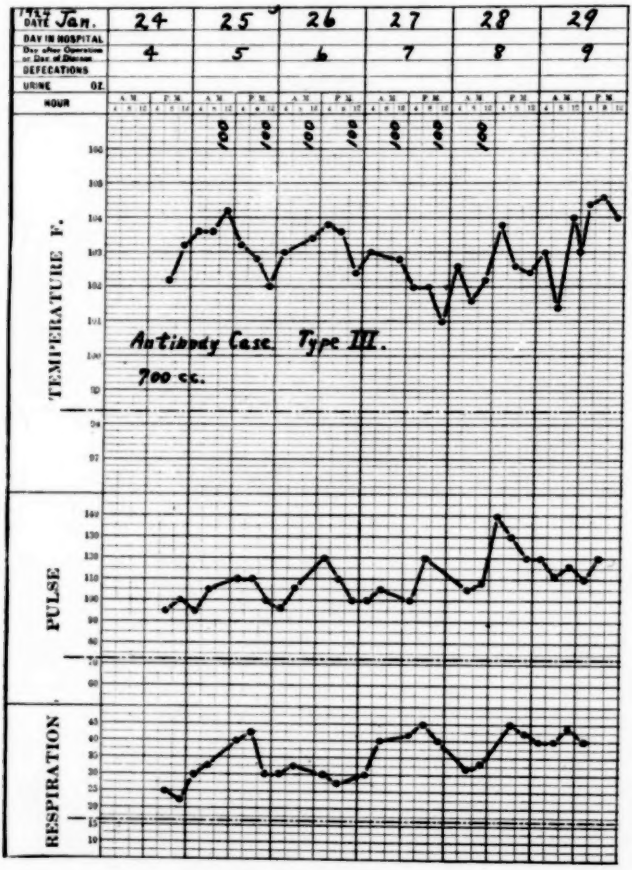

Fig. 9.—Temperature, pulse and respiration in Case 17.

CASE 2.—A man, aged 45, an Italian, with Type II pneumococcus pneumonia of the right upper and middle lobes, had marked tenderness in the gallbladder region with an icteric tinge to the skin of the thorax and the abdomen. At 3 p. m., 200 c.c. of antibody solution was given subcutaneously in the left axilla without reaction. At 12 p. m., 150 c.c. was given subcutaneously. One-half hour later, there was a severe chill lasting twelve minutes, followed by a temperature of 106.2 F. (rectal), then a sharp fall of temperature to 101,

at 4 a. m., and 99.2, at noon. The abdomen was softer and the right hypochondrium less sensitive.

This case shows a striking response to antibody treatment and illustrates the best clinical result obtained in the series.

CASE 6.—A man, aged 33, an American, who suffered from chronic alcoholism, had pneumococcus Type II pneumonia of the left lower lobe. The patient was given 625 c.c. of antibody solution. Although this case shows no sudden marked drop in temperature, the general condition, on the eighth and ninth days, was

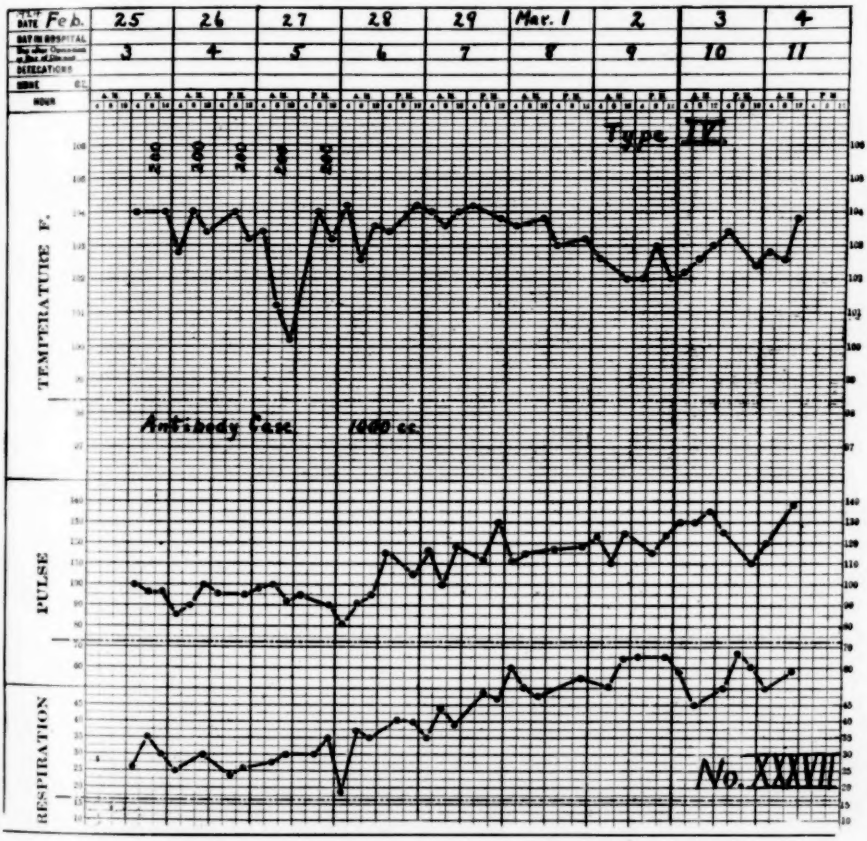
DAY DATE Feb. 25 26 27 28 29 Mar. 1 2 3 4
DAY IN HOSPITAL 3 4 5 6 7 8 9 10 11
HOUR
TEMPERATURE F.
PULSE
RESPIRATION
Type II.
Antibody Case. 1000 cc.
No. XXXVII.

Fig. 10.—Temperature, pulse and respiration in Case 37.

unusually good, considering that the patient suffered from chronic alcoholism and that the pneumonia precipitated an attack of delirium tremens which was so marked that he had to be restrained.

CASE 17.—A man, aged 21, a Porto Rican, with a pneumococcus Type III pneumonia of the right lower lobe was admitted on the fourth day of the disease. The fifth day, blood culture showed a few colonies of hemolytic streptococcus. He received 100 c.c. polyvalent antibody solution every twelve hours for seven doses. By the seventh day, there were signs of extension to

the right middle and right upper lobes. Blood culture, the ninth day, was sterile. He died, the ninth day, of myocardial failure. There was no response to phlebotomy and all the cardiac stimulants.

In this case, there was no notable improvement under antibody treatment, and the process extended rapidly.

Case 37.—A man, aged 26, a Swiss, was admitted with a Type IV pneumococcus pneumonia of the right lower lobe. After 800 c.c. of antibody solution,

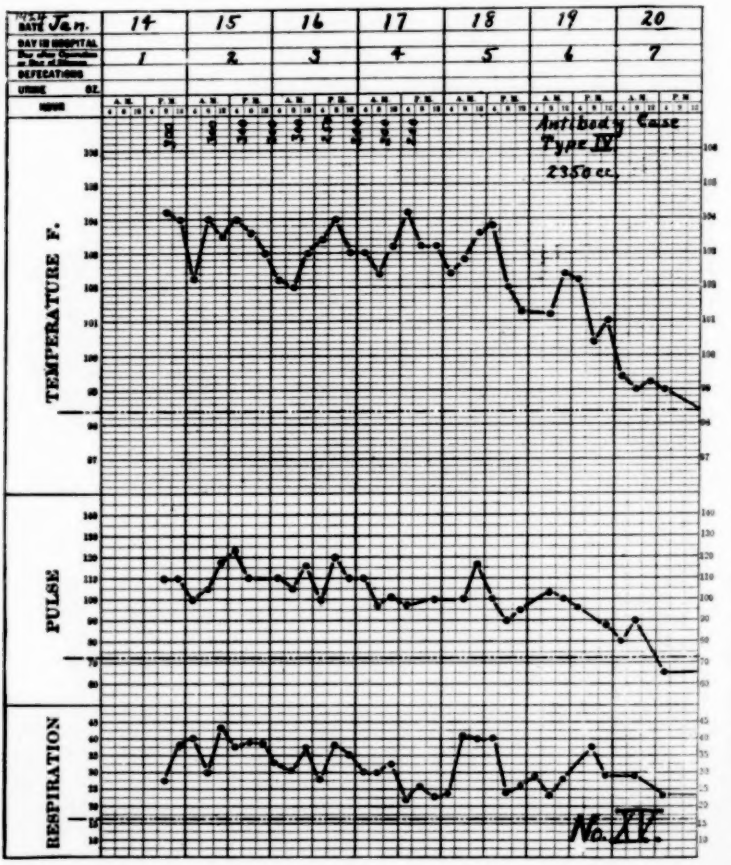

Fig. 11.—Temperature, pulse and respiration in Case 15.

the temperature had fallen to 100.2 F.; the pulse was 95, and respiration was 30. The night of the fifth day, the temperature had returned to 104. The sixth day, the right middle lobe was involved, and the seventh day, the left lower lobe as well. The eleventh day, the patient died of myocardial failure. Blood culture on the fourth day was sterile, and on the eighth day showed one colony per cubic centimeter of pneumococcus Type IV. Material obtained from the chest by postmortem puncture also showed a Type IV pneumococcus.

In this case, the progress was not influenced in any way, and the disease spread from one lobe to another in spite of vigorous antibody treatment.

CASE 15.—A man, aged 28, an American, with a pneumococcus Type IV pneumonia of the right middle and upper lobes, received nine doses of antibody solution, totaling 2,350 c.c., after which it was discontinued. This was a case which was obtained on the first day of the disease, the onset with chill occur-

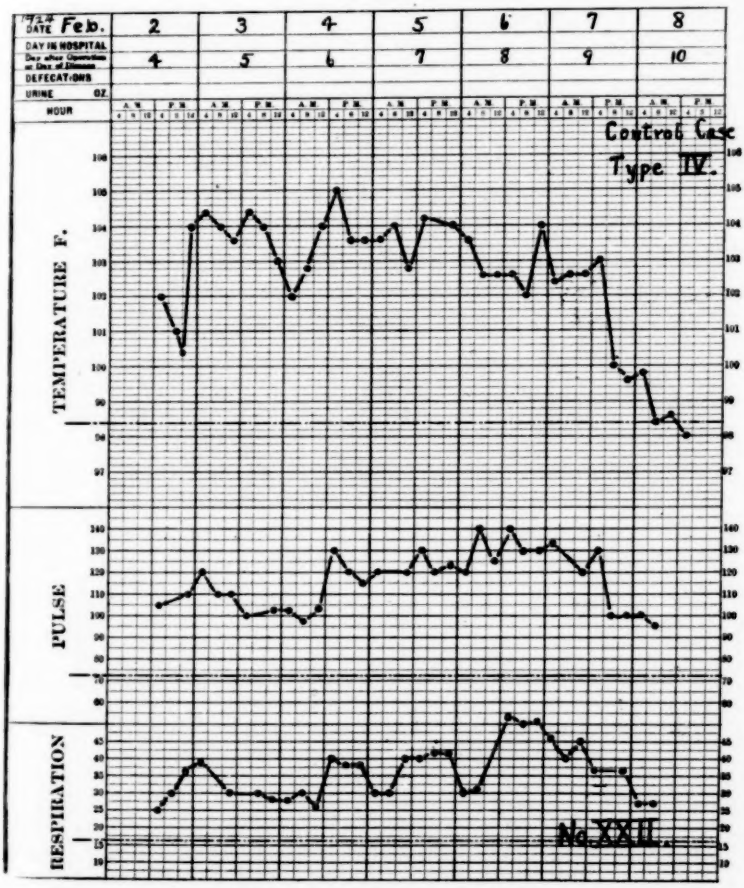

Fig. 12.—Temperature, pulse and respiration in Case 22.

ring at noon, and the patient being admitted to the hospital at 7:55 p. m. In spite of vigorous antibody treatment, the process was not halted in the lobe originally involved, but, the fifth day, it extended to the right upper lobe and went on, ending by lysis on the seventh day.

CASE 22.—A man, aged 25, a Spaniard, with a right lower lobar pneumonia, was admitted, the fourth day of the disease, and the crisis occurred, the ninth day. There were no complications of any sort.

SUMMARY AND CONCLUSIONS

1. The subcutaneous administration of pneumococcus antibody solution is attended by a very low incidence of thermal reactions as compared with its intravenous use, as reported by Cecil and Larsen, and Conner.

2. The subcutaneous injection of pneumococcus antibody solution invariably produces a painful tissue reaction, and this may persist for days.

3. The subpectoral region seems to be the most favorable site for injecting pneumococcus antibody solution.

4. In our series of twenty-three cases treated by antibody solution, only four cases gave evidence of subjective and objective improvement, while the remaining nineteen cases, in our opinion, did not appear to be benefited by it.

5. Pneumococcus antibody solution administered subcutaneously did not, in our very limited experience, tend to sterilize the blood stream.

6. Subcutaneous antibody treatment is of less value in Type I pneumococcus infections than is Type I pneumococcus antiserum administered intravenously.

7. Subcutaneous antibody treatment does not appear to prevent extension of the pneumonic process from one lobe to another.

8. The best results were obtained in Type IV pneumococcus pneumonias in which the subcutaneous antibody treatment registered a mortality of 10 per cent. as compared to a mortality of 21.42 per cent. in the control Type IV cases. If these results were due to antibody solution, it would seem probable that they were attributable to a nonspecific action of the solution.

Book Reviews

DIFFERENTIAL DIAGNOSIS. VOL. II. By RICHARD C. CABOT, M.D., Professor of Medicine and of Social Ethics at Harvard University. Third Edition. Cloth. Price, $9.00. Pp. 709; 254 illustrations. Philadelphia: W. B. Saunders Company, 1924.

This edition represents an amplification of the cases in former editions. Three hundred and seventeen cases are analyzed and discussed in a quite novel manner, and are grouped according to symptomatology and physical findings. It is composed of nineteen chapters, a large portion of the work being devoted to abdominal tumors and enlargements and to such topics as vertigo, dyspepsia, diarrhea and edema. The book is printed in large type on good paper and is profusely illustrated. It is very readable, and contains a great amount of information gained from a large experience. It should be particularly valuable to the general practitioner in medicine.

CLINICAL AND EXPERIMENTAL STUDIES OF THE OBSTETRICAL PALSIES OF PLEXUS BRACHIALIS. By S. G. K. BENTZON. Copenhagen: Levin and Munksgaard, 1922.

After an extensive discussion of the literature on the symptomatology, etiology and pathology of birth palsies, Bentzon concludes that overstretching of the brachial plexus is the chief cause of the Duchenne-Erbs type, thereby endorsing the opinion of Clarke, Taylor and Trout. It is caused by lesions of the fifth and sixth cervical roots near the junction of these roots. The author made many anatomic and experimental studies in order to determine the reason for the peculiar distribution of the paralysis among the many muscles that are innervated by these nerves. The most constant finding is the fixation of the arm in inward rotation due to the fact that the subscapularis muscle is unaffected. It was found that the scaleni protected the proximal portions of these nerves against pressure; that traction on peripheral nerves is easily transmitted to the plexus, even to the roots; that by the use of a special apparatus by means of which the distance between the mastoid process and the homolateral acromioclavicular joint could be increased in stillborn children, and by careful dissection, the entire plexus was easily exposed so that, in the various manipulations, degrees of stretching, place of rupture of nerves and probable manner of occurrence of these injuries were demonstrated. It is evident that when nerves are taut only slight amounts of pressure properly applied are necessary to cause great damage. The seven muscles most frequently affected in this type are innervated by the nerves which are shown to suffer the greatest stretching by this method.

The prognosis is considered as to the paralysis itself and as to the contractures with their sequelae. The prognosis is usually good because the lesion is due mainly to stretching and not to rupture of the nerves. Early treatment with physiotherapy influences the end-result greatly, particularly if begun before the development of contractures and deformities. The author discourages operations on the brachial plexus for relief of this condition.

Klumpke's type, i. e., lesions of the lower cervical and first dorsal nerves, is not discussed as fully as the Duchenne-Erb form. Pressure on or crushing of the nerves between the clavicle and the first rib apparently is the chief etiologic factor. Raising of the arms and shoulders, especially if the clavicle is elevated as well, causes great stretching of the lower nerves of the plexus,

notably the median and ulnar nerves. This type of palsy is more apt to occur in breech and face presentations. The prognosis is much less favorable in this type of palsy, and direct operations on the plexus are often indicated.

Very little is known of the pathology of either type because of the surprising paucity of necropsies.

The author presents thirty-one excellent case histories.

The various theories concerning palsies and the differential diagnosis of these conditions, as well as the physiology of the shoulder movement, are ably criticised and discussed.